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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. CORRELATION OF PLASMA CEA AND CEA TISSUE STAINING IN POORLY DIFFERENTIATED COLORECTAL CANCER.

Goslin R, O'Brien MJ, Steele G, Mayer R, Wilson R, Corson JM, Zamcheck N
(c/o Zamcheck) Mallory Gastrointestinal Res. Lab., Boston City Hosp., Boston, MA, 02118
Am J Med; 71(2):246-253 1981

A review of patients operated on for colorectal cancer disclosed poorly differentiated histologies in those whose preoperative and postoperative carcinoembryonic antigen (CEA) levels were not elevated, even in the presence of metastatic disease. CEA was, therefore, of little prognostic value o r predictive of disease recurrence in these patients. The amount of CEA in tumor tissue of 17 patients with poorly differentiated colorectal cancer was estimated with the immunoperoxidase staining technique and was correlated with histology and plasma CEA levels obtained during various stages of disease.

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Five tumors did not stain negatively for CEA and all had predominantly poorly differentiated histologies. In all of these patients metastatic disease developed but not elevated plasma CEA levels. In contrast 12 tumors stained positively for CEA and were found to contain either differentiated areas or signet ring cells. Serial plasma CEA levels correctly monitored the postoperative courses of all 12 patients. Six of these had a relapse and all were detected by serial increases in plasma CEA. The remaining six were disease free greater than 48 mo after resection and had normal plasma CEA levels. Among poorly differentiated tumors, those that contain gland-forming areas of signet ring cells can be assumed to produce CEA, and plasma CEA levels can be used effectively for monitoring. On the other hand, undifferentiated tumors which do not stain for CEA identify those patients whose plasma CEA levels do not provide a useful monitor. (Author abstract) (25 Refs)

2. LOCALIZATION AND CONCENTRATION OF CARCINOEMBRYONIC ANTIGEN (CEA) IN GASTROINTESTINAL TUMORS: CORRELATION WITH CEA LEVELS IN PLASMA.

Wagener C, Muller-Wallraf R, Nisson S, Groner J, Breuer H
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JNCI; 67(3):539-547 1981

In 50 patients with gastrointestinal carcinomas, the following tumor parameters were studied: the concentration and localization of carcinoembryonic antigen (CEA) in tissue, extension, invasion, infiltration, differentiation, and necrosis. CEA concentrations were measured in plasma samples of all patients. In seven patients with gastric carcinomas, CEA concentrations in tissue were low. Generally, only single cells or cell groups were CEA-positive. Elevated CEA levels in plasma resulted mainly from distant metastases and not from the primary tumor. In 43 colorectal carcinomas, CEA concentrations in tissue varied between 1.5 and 472 ug/g tissue. They were closely related to the degree of accumulation of CEA-positive necrotic material in the neoplastic glands. In 35 patients with colorectal carcinomas without CEA producing distant metastases, preoperative CEA levels in plasma were normal when tumor necrosis and perineural invasion were absent and CEA concentrations in tissue were low. CEA levels in plasma were regularly elevated when the tumor showed considerable necrosis in the presence of high CEA concentrations in tissue. (Author abstract) (22 Refs)

3. PLASMA CARCINOEMBRYONIC ANTIGEN IN THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH HEPATOCELLULAR CARCINOMA.

Melia WM, Johnson PJ, Carter S, Munro-Neville A, Williams R
Liver Unit, King's Coll. Hosp. and Medical Sch., Denmark Hill, London SE5 8RX, England
Cancer; 48(4):1004-1008 1981

The value of serial carcinoembryonic antigen (CEA) measurements as a marker of disease progression or in monitoring treatment was investigated in patients with hepatocellular carcinoma. Of 40 patients, including 16 with normal serum alpha-fetoprotein (AFP) concentrations, 29 (72.5%) had abnormal plasma CEA at presentation. Although this was more common in patients with pre-existing cirrhosis, the mean and range of plasma CEA were similar in patients with and without pre-existing hepatic disease. There was no correlation between plasma CEA and any biochemical parameter of hepatic function, although plasma CEA concentrations were significantly lower in patients with well-differentiated tumors. CEA concentrations increased in 71% of patients who had no response to cytotoxic drugs, but CEA also increased in 62.5% of those patients who did respond. Plasma CEA concentrations were elevated in 62.5% of patients with normal and 79% of patients with raised serum AFP on admission to the hospital. There was no correlation between individual AFP and CEA concentrations. Although elevated plasma CEA levels may be of diagnostic value in patients with hepatocellular carcinoma in the absence of pre-existing hepatic disease, and in those with normal serum AFP, our findings indicate that it does not behave as a true tumor marker. (Author abstract) (11 Refs)

4. CARCINOEMBRYONIC ANTIGEN LEVELS AS AN INDICATOR OF THE PRIMARY SITE IN METASTATIC DISEASE OF UNKNOWN ORIGIN.

Koch M, McPherson TA
Dept. Medicine, Cross Cancer Inst., 11560 University Ave., Edmonton, Alberta, T6G 1Z2, Canada
Cancer; 48(5):1242-1244 1981

In 542 patients with metastatic disease arising from a known primary site, elevated CEA levels (greater than 10 ng/ml) were most often associated with metastatic disease originating from entodermally derived organs, breast, and mucinous ovarian primaries. This observation held true, in general, in a small series of 32 patients with metastatic disease arising from a primary site that had been unknown, but that was eventually identified. Thus, although a CEA level below 10 ng/ml is of no use in pointing to a particular primary site, a value above 10 ng/ml suggests the site is more likely to be in an entodermally derived organ, breast or ovary containing a mucinous carcinoma. If liver metastases are present, there is an increased probability that the primary site will be found in the large bowel or pancreas. (Author abstract) (9 Refs)

5. MICROHETEROGENEITY OF ALPHA-FETOPROTEIN IN PATIENT SERUM AS DEMONSTRATED BY LECTIN AFFINO-ELECTROPHORESIS.

Breborowicz J, Mackiewicz A, Breborowitz D
Dept. Pathological Anatomy, Inst. Biostructure, 49, Przybyszewskiego St., 60355 Poznan, Poland
Scand J Immunol; 14(1):15-20 1981

Microheterogeneity of alpha-fetoprotein (AFP) present in the sera of 76 patients was studied by lectin affino-immunoelectrophoresis. Seventeen patients had benign liver disorders and the remaining 59 patients were treated for primary or secondary liver cancer or yolk sac tumor. By means of Con A, AFP was divided into two variants, while lentil lectin (LCA) made it possible to separate AFP in three variants. In some patients the relative concentrations of Con A and LCA AFP variants were similar; these patients were believed to produce AFP of the same 'profile'. Fourteen AFP profiles were observed by estimation of the area enclosed by precipitates corresponding to respective AFP variants. It was also possible to estimate the AFP profile on the basis of a simple visual analysis of the electrophoretic plates. The obtained results indicate that the AFP profiles of patients with cancer were variable. In spite of variations of the AFP profile in cancer patients, in most cases it was possible to differentiate primary liver cancer from yolk sac tumor and from liver metastases of cancer. In addition, in two-thirds of hepatoma patients the AFP profile was different from the profile observed in patients with benign liver disorders. (Author abstract) (17 Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

6. DIAGNOSTIC VALUE OF GAMMA GLUTAMYL TRANSFERASE IN THE DIAGNOSIS OF LIVER METASTASES OF MALIGNANT TUMORS.

Pejchl S, Chaloupka F
Vnitrni klinika, Fakulta detskeho lekarstvi Karlovy university, Vlasska 36, 118 33 Prague 1, Czechoslovakia
Vnitr Lek; 27(6):605-610 1981

The value of the determination of the gamma glutamyl transferase (GGT) activity in the blood serum in the diagnosis of hepatic metastases of extrahepatic malignant tumors was studied in 222 tumor patients. The GGT activity was increased in 89.7% of the patients with hepatic metastases and in 88.9% of those without hepatic metastases among the icteric patients, i e., the GGT test had practically no diagnostic value. Among the anicteric patients, the GGT activity was increased in 82.7% of the cases with hepatic metastasis and in 36.8% of the cases without hepatic metastasis. Normal GGT activity in anicteric patients was a better indicator of the absence of liver metastasis than was increased GGT activity an indicator of metastasis. The findings indicate that GGT is not a specific but a sensitive indicator of hepatic metastases. (24 Refs) (In CZE)

7. TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE-CONTAINING CELLS IN PERIPHERAL BLOOD: IMPLICATIONS FOR THE SURVEILLANCE OF PATIENTS WITH LYMPHOBLASTIC LEUKEMIA OR LYMPHOMA IN REMISSION.

Froehlich TW, Buchanan GR, Cornet JM, Sartain PA, Smith RG
(c/o Smith) Cancer Center, Univ. Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX, 75235
Blood; 58(2):214-220 1981

An indirect immunofluorescence assay was used to quantitate TdT-containing (TdT+) cells in the mononuclear WBC fraction of peripheral blood from normal subjects and patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL). In normal children (10) and adults (10), 0.036% +-0.014% (mean +- SD) and 0.030% +-0.015% TdT+ cells were found. In peripheral bloods from 10 children receiving chemotherapy for tumors other than ALL or LL, 0.040% +-0.039% TdT+ cells were found. Serial determinations were performed on 15 patients with ALL or LL who were in clinical remission. Eight of these patients remained in continuous remission and always had fewer than 0.11% TdT+ cells in their peripheral blood. Three patients who developed systemic relapse were found to have progressively rising numbers of TdT+ cells in their peripheral blood prior to clinical evidence of relapse. All three of these patients had greater than 0.1% TdT+ cells in their peripheral blood from 3 to 8 wk prior to clinical relapse. In three other patients, localized extramedullary relapse developed, but no trend was found on serial TdT determinations. Thus, the indirect immunofluorescence assay for TdT detects a small population of cells in normal peripheral blood. In patients with ALL, progressive increases above this normal level were associated with subsequent bone marrow relapse. (Author abstract) (17 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

8. ESTROGEN RECEPTOR STATUS AS A PROGNOSTIC INDICATOR FOR STAGE I BREAST CANCER PATIENTS (MEETING ABSTRACT).

Crowe J, Hubay C, Pearson O, Marshall J, McGuire W
Departments of Surgery and Medicine, Case Western Reserve University, University Hospitals, Cleveland, OH, 44106
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

Women with Stage I breast cancer have a more favorable prognosis than those with Stage II disease. Estrogen receptor (ER) content of the primary tumor has allowed prognostic discrimination of Stage II patients. ER- Stage II patients have more rapid recurrence (p less than .001) and poorer survival (p less than .001) than ER+ patients. This study focuses on the prognostic significance of estrogen receptor (ER) determination in 509 Stage I patients. Each patient had total mastectomy with axillary dissection and assays to determine the ER receptors of the primary tumor. At 49 mo median follow-up, there is a 16% recurrence. Premenopausal patients are recurring more rapidly than post menopausal patients, ER- patients are recurring more rapidly than ER+ patients (p equals .0117) and have worse survival (89% vs 95%, p equals .0157). ER- and ER+ premenopausal patients are recurring at a similar rate. In the postmenopausal group, ER- patients are recurring more rapidly than ER+ patients at 51 mo (29% vs 13%). The results of this study emphasize that hormone receptor assays have prognostic value for recurrence and survival of Stage I breast cancer patients. (no Refs)

9. THE PROGNOSTIC VALUE OF THE ESTROGEN RECEPTOR (ER) LEVEL IN PATHOLOGIC STAGE (PS) I AND II ADENOCARCINOMA (CA) OF THE BREAST (MEETING ABSTRACT).

Bitran JD, Shapiro CM, Schifeling D, Desser RK, Rochman H, Michel A, Shapiro R, Evans R, Kozloff AA, Billings AA
Michael Reese Medical Center, University of Chicago, Chicago, IL
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

Recent studies have shown that the level of ER in patients (pts) with CA of the breast may be an important prognostic variable in predicting early recurrence. Pts with lower levels haves been reported to have shorter disease free interval than pts with high levels. Few studies have examined the prognositc value of ER in pts treated with adjunctive chemotherapy. Since 1974 we have been prospectively evaluating the ER level as an indicator of early relapse. From 1974 to 1979, 302 consecutive pts (73 premenopausal, median 46 yr, 229 postmenopausal, median 62 yr) with PS I (185 pts) and PS II (117 pts) had ER levels performed. All pts were treated with a modified radical mastectomy and in pts with positive nodes, PS II, adjunctive chemotherapy was administered. All pts have been followed from 12 to 60 mo, median 40 mo. Of the 302 pts, 147 were ER positive, 155 ER negative. ER status was not predictive or relapse in either PS I or PS II pts. A multivariant analysis of tumor size, nodal status (0,1-3, greater than 3), age, and ER level, disclosed only tumor size and nodal status to be important prognostic variables predicting relapse. In light of conflicting reports, ER status cannot be used as a prognostic determinant at this time. (no Refs)

10. VARIABILITY OF STEROID RECEPTORS IN MULTIPLE BIOPSIES OF BREAST CARCINOMA (MEETING ABSTRACT).

Lee YT
University of Southern California School of Medicine, Los Angeles, CA, 90033
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

From 1975 to 1980, estrogen receptor (ER) level was measured on specimen taken from 350 patients with carcinoma of the breast at LAC-USC Medical Center (139 also had progesterone receptor analyzed). There were 53 patients who had two or more specimen studied. Among the 32 who had no interval therapy, 25 patients had repeated tests within one mo, only two had reversal of ER results. Among 7 pts who had ER tests 9-36M apart, 3 of 4 ER(+) lesions had ER(-) metastasis. Among the 21 patients who received systemic therapy, 3 of 10 ER(+) became ER(-), while 2 of 11 ER(-) became ER(+). Specifically, the ER levels increased in 3 patients who failed hormonal manipulation, but decreased in a fourth patient who failed tamoxifen. Among 10 patients who had 3-9M of pre-operative cyclophosphamide, methotrexate, 5-fluorouracil (CMF) therapy, only one had reversal of ER result (biopsy ER+, mastectomy ER-). Although this is a relative small series, our data do suggest that: (1) there is more variability when comparing specimen taken after longer intervals, (2) both hormonal and cytotoxic treatment may effect steroid receptor levels. (no Refs)

11. MULTIPLE SIMULTANEOUS AND SEQUENTIAL ESTROGEN RECEPTOR VALUES IN PATIENTS WITH BREAST CANCER (MEETING ABSTRACT).

Peetz ME, Nunley DL, Moseley HS, Keenan EJ, Davenport CE, Fletcher WS
Division of Surgical Oncology, Department of Surgery, University of Oregon Health Sciences Center, Portland, OR, 97201
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

Estrogen receptors (ER) and progesterone receptors are frequently used to determine the most appropriate method of therapy for women with disseminated breast carcinoma. It is important to determine if they are reproducible when measured in multiple sites of metastasis and if they accurately reflect the hormonal status of the tumor. It is also important to know whether receptor values and hence, the hormonal sensitivity of the tumor changes over the course of time with and without therapy. Fifty-nine women had multiple estrogen receptor assays done, either simultaneously or sequentially. Eighty-six percent of patients who had multiple synchronous ER assays from various metastatic sites showed no significant discrepancies in ER values. When estrogen receptor assays were done sequentially without intervening therapy, 83 percent of the patients maintained their initial positivity or negativity. Intervening chemotherapy also had no effect on sequential assays. However, when the second estrogen receptor determination was preceded by hormonal manipulation, 33 percent of the patients had a significant discrepancy in ER values. Among eleven patients who had a rise in absolute ER values, the response to hormonal manipulation was 80 percent. The most common discrepancy, a decrease in absolute ER value, did not correlate with an increased response to endocrine manipulation. (no Refs)

12. EFFECT OF PRESURGICAL RADIOTHERAPY ON THE STEROID RECEPTOR CONCENTRATIONS IN PRIMARY BREAST CARCINOMA.

Janssens JP, Bonte J, Drochmans A, Muller J, Rutten J, Wittevrongel C, De Loecker W
(c/o De Loecker) Afdeling Biochemie, Campus Gasthuisberg, Herestraat, B-3000 Leuven, Belgium
Eur J Cancer; 17(6):659-664 1981

With age, estradiol receptor concentrations increased in primary breast carcinoma while age did not seem to affect the progesterone receptor levels. Above the age of 70, all tumors examined proved to be hormone-dependent. Analysis by light microscope did not allow correlation of the receptor-positive tumors to any specific or predominant cellular structure. Presurgical radiotherapy of 20 gray significantly reduced the estradiol and to an even greater extent the progesterone receptor concentrations in the tumors. Prebioptic irradiation with 8 gray accentuated the inhibition of steroid receptor proteins. This reduction in receptor concentration after radiotherapy should be taken into account when interpreting steroid receptor values. (Author abstract) (37 Refs)

13. DISTRIBUTION OF STEROID HORMONE RECEPTORS IN HUMAN SOFT TISSUE SARCOMAS.

Chaudhuri PK, Walker MJ, Beattie CW, Das Gupta TK
Dept. Surgery, Div. Surgical Oncology, Univ. Illinois Medical Center, 840 South Wood, Chicago, IL, 60612
Surgery; 90(2):149-153 1981

Sixty-six human soft-tissue sarcoma specimens were assayed for incidence and distribution of steroid hormone receptors. Liposarcomas (43%) and leiomyosarcomas (60%) had a high incidence of estrogen receptor. In contrast, sarcomas of fibrous and synovial tissue origin lacked any detectable receptor for estrogen. Malignant fibrous histiocytoma had the highest incidence of glucocorticoid (66%) and androgen (66%) receptors. The incidence of receptors for estrogen and glucocorticoid was higher in female than in male patients (62% and 38%, respectively). Sucrose density gradients demonstrated 8s-type receptors for both estrogen and glucocorticoid. Data from this study suggest that specific high-affinity cytosolic receptors for steroid hormones are present in human soft tissue sarcoma and that their distribution may depend on the histogenetic origin and the sex of patients. (Author abstract) (11 Refs)

14. PLASMA CALCITONIN AS A MARKER OF DISEASE ACTIVITY IN PATIENTS WITH SMALL CELL CARCINOMA OF THE LUNG.

Wallach SR, Royston I, Taetle R, Wohl H, Deftos LJ
(c/o Deftos) 111C, Veterans Admin. Medical Center, 3350 La Jolla Village Drive, San Diego, CA, 92161
J Clin Endocrinol Metab; 53(3):602-606 1981

To evaluate the usefulness of plasma calcitonin as an index of tumor burden and disease activity, we undertook a prospective study of serial calcitonin measurements in a group of patients with small cell carcinoma of the lung from diagnosis throughout a period of intensive therapy. Plasma calcitonin was significantly elevated in 84% of patients with extensive small cell carcinoma of the lung and was not elevated in patients with limited disease at the time of diagnosis. The elevated values fell significantly in response to chemotherapy and radiation therapy, and reflected regression of followable disease and improvement in clinical status. A significant correlation existed between plasma calcitonin and extent of disease. Relapse was generally associated with an increase in elevated plasma

calcitonin levels, and calcitonin appeared to reflect tumor burden. The serial measurement of plasma calcitonin is useful in the management of the patient with small cell carcinoma of the lung. (Author abstract) (16 Refs)

15. ASYMPTOMATIC DEXAMETHASONE NON-SUPPRESSIBLE ACTH AS A TUMOR MARKER (MEETING ABSTRACT).

Varsano-Aharon N, Urivetzky M
Division of Adult Endo., L. I. Jewish-Hillside Medical Center, North Hyde Park, NY, 11042
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

We have exploited the presumed autonomy of tumor ACTH production and measured ACTH in plasma under conditions of dexamethasone suppression as a means of separating the pituitary from the ectopic product. An antiserum with N-terminal specificity known to detect all currently described ACTH prohormonal forms was used. Plasma and urinary cortisol measurements were used as in-vivo assay for ACTH biological activity. A dissociation of immunological from biological activity in the form of a high ACTH/cortisol ratio was interpreted as evidence of circulating ectopic ACTH. We have studied 87 patients with a variety of epithelial and lymphatic tumors without the clinically recognizable syndrome of ectopic hormone production. Patients with benign tumors and noncancerous proliferative conditions were studied as matched controls. Random ACTH and cortisol levels were determined under basal conditions and following 2 days of standard high-dose dexamethasone suppression. The random ACTH levels in the control groups was indistinguishable from those of 24 healthy adults. The basal ACTH levels of cancer patients showed a wide scatter and a mean of 2 standard deviation over the mean for controls. The highest levels were associated with amine-precursor uptake decarboxylation (APUD) tumors and epidermoid lung cancer. Significantly better discrimination between cancer patients and controls was achieved with dexamethasone administration. Normals and controls showed maximal suppression of both ACTH and cortisol with ACTH/cortisol ratio unchanged. A total of 32% of the cancer patients had ACTH non-suppressibility, but maximal cortisol suppression. The ACTH cortisol ratio increased from a random mean of 2.57 +/-3.31 to 21 +/-15. Two patients with APUD tumors and random levels in excess of 250 pg/ml showed high degree of ACTH suppressibility. (no Refs)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

16. ANALYSIS OF CELL-SURFACE ANTIGEN OF HAIRY CELL LEUKEMIA (HCL).

Ogasawara M, Ishii Y, Kikuchi K, Aikawa K, Mikuni C
First Dept. Pathology, Sapporo Medical Coll., Sapporo-shi, Hokkaido, 060, Japan
Igaku Ayumi; 116(1):29-31 1981

One patient with cell surface Ig-positive HCL and another patient with HCL shown to have B cell markers by immunoprecipitation with anti-HCG and anti-B serum were seen. An antiserum specific for hairy cells (AHCS) was obtained by immunizing rabbits with 2 x 10(7) hairy cells iv. The absorbed AHCS for both patients diluted 80-160x produced 100% fluorescein isothiocyanate-stained cells, but peripheral blood (T, B cells) and the two B-cell lymphoid leukemias were not responsive. Some tonsil B cells responded with fluorescence of 12-27%, but no T cells responded. Various leukemia cells other than the hairy cells barely responded to the lymphocytes, nor did they respond to the granulocyte or monocyte leukemia cells. The unabsorbed antiserum had four major peaks, with mol wt of 110,000-120,000, 94,000-96,000, 48,000-50,000, and 30,000-34,000 for I, II, III, and IV. In the absorbed AHCS, peaks II and IV disappeared, leaving only I and II. The antigen at peak III is considered to differ from histocompatibility antigen (HLA) because it is not absorbed by anti-HLA or anti-beta2m. This antigen is considered to be the one that is differentiated from that of B cells which characterizes the hairy cell. The antigen at peak IV was also obtained by adding anti-B serum to the B cell lysates and the peak IV antigen that disappeared was considered to be an Ia-like antigen on the hairy cell. Antisera obtained from the two HCL patients were shown to recognize the same antigen. (Author abstract) (12 Refs) (In JPN)

17. A MONOCLONAL ANTIBODY AGAINST A BURKITT LYMPHOMA ASSOCIATED ANTIGEN (MEETING ABSTRACT).

Wiels J, Fellous M, Tursz T
No affiliation given
Immunobiol; 159(1/2):31 1981

A monoclonal antibody, referred to as 38.13, was obtained by fusing murine myeloma cells with Lewis rat splenocytes sensitized with Daudi cells (human Burkitt lymphoma, containing Epstein-Barr virus genome, but lacking HLA A, B, C and beta2 microglobulin molecules at the cell surface). 38.13 antibody was demonstrated to be a rat IgM. By complement-dependent microcytotoxicity and indirect immunofluorescence assays, 38.13 antibody was shown to react specifically with cells derived from Burkitt tumors, including both Epstein-Barr virus genome carrying and Epstein-Barr virus negative Burkitt lymphoma. By contrast Epstein-Barr virus containing lymphoblastoid cell lines, derived from normal B lymphocytes, were not recognized by 38.13 antibody. Malignant fresh cells from patients affected with various lymphoproliferative disorders were negative, except 4/8 cases of abdominal Burkitt-like lymphomas. Normal lymphocytes from peripheral blood, spleen, lymph node, tonsil and bone-marrow and mitogen (phytohemagglutinin, poke weed mitogen and Concanavalin A) activated blasts were also negative. Thus 38.13 antibody apparently recognized a Burkitt-associated antigen, which is clearly not related to Epstein-Barr virus. The pattern of reactivity of 38.13 antibody with various Burkitt lymphoma cells appeared quite heterogenous, and some Burkitt were constantly negative. 38.13 antibody could thus define a peculiar subgroup of Burkitt lymphoma. (no Refs)

18. DIFFERENTATION PATHWAYS OF HUMAN LYMPHOCYTES: USE OF MONOCLONAL ANTIBODIES AND MALIGNANT T CELLS AS INVESTIGATIVE PROBES (MEETING ABSTRACT).

Haynes BF
No affiliation given
Immunobiol; 159(1/2):14 1981

Using a panel of 12 well characterized anti-human T cell monoclonal antibodies, the surface antigen pattern of thymocytes and normal peripheral blood (PB) cells, and PB cells or cell lines from patients with cutaneous T cell lymphoma (CTCL) or T cell acute lymphoblastic leukemia (ALL) have

been studied. T cell specific monoclonal reagents could be grouped as follows: Antibodies OKT6 and NA1/34 define a thymocyte specific antigen absent on normal PB T cell. Antibodies 17F12, T101, 10.2, and 9.6 define antigens present on most thymocytes and PB T cells. Antibodies 3A1, OKT4, and OKT8 define antigens on most thymocytes, but only on subsets of PB T cells, and antibodies OKT3 and A-50 define antigens on a subset of thymocytes and all PB T cells. CTCL cells were negative for the human thymus antigen defined by antibodies OKT6 and NA1/34 and positive for the pan-T cell antigens OKT3, A-50, 17F12, 10.2 and 9.6. Most importantly, all CTCL (Sezary) cells were positive for T helper cell subset antigens OKT4 and 9.3 and were negative for subset antigens 3A1 and OKT8. The T cell specific antibody 3A1 was the only monoclonal reagent which distinguished between CTCL T cells (3A1-) and T-ALL cells (3A1+). Moreover, antibody 3A1 was the most reliable T cell marker for T-ALL cells as it was the only T cell specific monoclonal reagent positive on all 15 T-ALL PB malignant cells or T-ALL cell lines tested. Thus, phenotypic characterization of cells derived from T cell malignancies has demonstrated that while T-ALL cells express any of a number of T cell antigen patterns, CTCL (Sezary) cells are remarkably homogeneous, and are derived from a well defferentiated OKT4+, 9.3+, 3A1-, OKT8-helper T cell subset. Phenotypic characterization of malignant T cell populations with anti-T cell monoclonal antibodies provides an important tool for dissecting apart distinct functional subsets of human T cells. (no Refs)

19. MONOCLONAL ANTIBODIES THAT DEMONSTRATE SPECIFICITY FOR SEVERAL TYPES OF HUMAN LUNG CANCER.

Cuttitta F, Rosen S, Gazdar AF, Minna JD
NCI-VA Medical Oncology Branch, Div. Cancer Treatment, NCI, Washington, DC, 20422
Proc Natl Acad Sci USA; 78(7,part2):4591-4595 1981

Monoclonal antibodies with selectivity for human lung cancer were produced by immunizing BALB/c mice with an established line of human small cell lung cancer (NCI-H69) and fusing the mouse spleen cells to mouse myeloma line X63-Ag8.653. The resulting hybrid cells were initially screened by immunoautoradiography for production of antibodies that would react with NCI-H69 and another small cell lung cancer line (NCI-H128) but not its autologous B-lymphoblastoid line (NCI-H128BL). Stable monoclonal antibody-producing lines were isolated by repeated cloning. Three independently derived monoclonal antibodies, designated 525A5, 534F8, and 538F12, were found to react with three of the major types of human lung cancer (small cell, adenocarcinoma, and squamous carcinoma). They did not react with bronchioloalveolar and large cell lung cancers, myeloma, lymphomas, leukemias, osteogenic sarcoma, mesothelioma, hypernephroma, malignant melanoma, simian virus 40-transformed human fetal lung cells, skin fibroblast lines, human B-lymphoblastoid lines, human RBC, and rodent cells. Interestingly, these antibodies also bound to three out of three human neuroblastomas and two out of three breast cancers but failed to react with mouse neuroblastoma and rat pheochromocytoma. The monoclonal antibodies reacted with human small cell lung cancer tumors obtained at autopsy, but had insignificant reactions with normal human lung, liver, spleen, and skeletal muscle. We conclude that monoclonal antibodies have been generated that react with common antigenic determinants expressed on several human lung cancer types, neuroblastoma, and some breast cancers, but are not detectable by our current assays on a variety of other human tumors or normal adult human tissues. Such antibodies are of potential clinical and biological importance. (Author abstract) (50 Refs)

20. STRUCTURAL CHARACTERIZATION OF HUMAN MELANOMA-ASSOCIATED ANTIGEN P97 WITH MONOCLONAL ANTIBODIES.

Brown JP, Nishiyama K, Hellstrom I, Hellstrom KE
Div. Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Immunol; 127(2):539-546 1981

Monoclonal antibodies were used to study p97, a human melanoma-associated antigen (MAA). Four hybridomas, designated 4.1, 96.5, 118.1, and 8.2, were obtained by fusing mouse myeloma cells with spleen cells from mice immunized with human melanoma cells. Antibodies 4.1 and 8.2 were IgG1; antibodies 96.5 and 118.1 were IgG2a. Sequential immunoprecipitation (IP) and sodium-dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) showed that all four antibodies recognized the same 97 kilodalton (kD) protein. Binding studies with 125I-labeled antibody showed that antibodies 4.1 and 96.5 bound the same epitope, p97a. Antibodies 118.1 and 8.2 defined epitopes p97b and p97c, respectively. Six monoclonal antibodies (M17 , L1, L10, R10, I12, and K5) specific for gp95, a 95 kD melanoma cell surface glycoprotein were also tested. Sequential IP showed that these antibodies bound p97; p97 and gp95 are thus identical. Binding studies showed that antibody M17 bound epitope p97a, and antibodies L1, L10, and R19 bound epitope 97c. Antibodies I12 and K5 defined two other epitopes, p97d and p97e, respectively. SDS-PAGE under on reducing conditions indicated that p97 is monomeric, probably with intrachain disulfide bonds. Cell-surface labeling of sialic acid residues and neuraminidase digestion showed that p97 is a sialoglycoprotein. Digestion of p97 with papain or trypsin produced a stable 40 kD fragment, which expressed epitopes p97a, p97b, and p97c, but not p97d or p97e. (Author abstract) (35 Refs)

21. REACTIVITY OF ANTISERA TO ANTIGENS OF C-TYPE VIRUSES WITH LEUCOCYTES FROM PATIENTS WITH ACUTE LEUKAEMIA.

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Pathology; 13(2):289-298 1981

A number of previous studies have suggested that certain C-type viruses from non-human primates are associated with acute leukemia in humans. The present study sought to examine this association further by detection of antigens related to these viruses on the surface of acute leukemia cells. Antisera against the whole viruses or the major internal protein of simian sarcoma, endogenous baboon and Rauscher viruses were tested against mononuclear cells from patients with acute leukemia at various stages of their disease in 51Cr release WBC dependent cytotoxic assays. A high proportion of the patients had antigens related to these viruses detectable on their blood WBC at some stage in their disease whereas with one exception blood WBC from non-leukemic subjects did not. The expression of these antigens did not show a close relation to the number of blast cells in blood detected on morphological grounds. Antigens related to the non-human primate viruses were detected on mononuclear cells from bone marrow samples of several non-leukemic patients which indicated they were not specifically associated with leukemia. Antigens related to the Rauscher virus were detected on cells of practically

all bone marrow samples tested. These results suggest that assays to detect these antigens would be of limited usefulness to monitor disease activity in patients with acute leukemia. Their expression on blood WBC however appeared strongly associated with acute leukemia and further studies to assess the prognostic and epidemiological significance of detection of these antigens appears warranted. (Author abstract) (16 Refs)

22. BINDING OF PEANUT LECTIN TO GERMINAL-CENTRE CELLS: A MARKER FOR B-CELL SUBSETS OF FOLLICULAR LYMPHOMA?

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Br J Cancer; 44(1):68-74 1981

The binding of horseradish-peroxidase-labeled peanut lectin (HRP-PNL) to cryostat sections of tonsil, lymphoma lymph nodes, reactive lymph nodes and miscellaneous tumors demonstrated that PNL binds selectively to lymphocytes in germinal centers. Lymph nodes from 21 patients with non-Hodgkin's lymphomas were phenotyped as cell suspensions for PNL binding, and the following surface markers: E rosetting, C3d, SIg, OK markers of T-cell subsets, Ig heavy-chain and light-chain classes. There was a positive correlation between PNL binding and cells with SIg and C3d receptors. 4/5 cases of centroblastic/centrocytic follicular lymphoma had a PNL+ Sig+ C3d+ phenotype. Both cases of centroblastic/centrocytic diffuse lymphoma were PNL-. There was no correlation between PNL binding and heavy- or light-chain Ig class. PNL binding and presence of C3d receptors were not always positively correlated, indicating that follicular cells may be either PNL+ SIg+ C3d+ or PNL+ SIg+ C3d-. The binding pattern of PNL to one case of thymic hyperplasia and two cases of malignant lymphoma lymphoblastic T type suggested that some but not all cortical thymocytes bind PNL. (Author abstract) (9 Refs)

23. CHRONIC LYMPHOCYTIC LEUKEMIA OF TG-TYPE WITH NK- AND ADCC- ACTIVITY: DEMONSTRATION OF T-LYMPHOCYTIC AND MONOCYTIC ANTIGENS (MEETING ABSTRACT).

Thiel E, Stunkel K, Rieber EP, Rodt H, Thierfelder S, Feucht H, Meier CR, Goldstein G, Kung PC, Schlimok G
Institut fur Hamatologie, Munich, W. Germany
Immunobiol; 159(1/2):141 1981

Routine typing tests of a patient with a chronic lymphocytic leukemia (CLL) revealed at T-cell type of the leukemia cells (484,000 mm(3)). The cells with abundant cytoplasm containing agurophilic granules and acid phosphatase activity had strong FcIgG, but no FcIgM receptors. They exhibited both natural killing (NK) activity and antibody dependent cytotoxicity (ADCC) when tested with unsensitized or sensitized melanoma target cells. They did not suppress nor support B-lymphocyte differentiation into plasma cells and analyzed in a pokeweed mitogen (PWM)-stimulated system. Repeated analyses of the leukemia cell phenotype with monoclonal anti-WBC antibodies by quantitative fluorescence and autoradiographic methods revealed a strong reaction with the Pan-T reagents OKT3 and Lyt 3, but not with Leu-1 nor with Lyt 2 that usually stains CLL of B cell type. Completely negative were OKT 4 (specific for helper cells) and OKT 6, 9, 10 (specific for thymic phase), whereas a weak reaction of OKT 5 (specific for suppressor cells) with around 30 percent of the cells was noted. Ia-like antigens were not expressed. A very strong reaction with OKT8 (reacts with OKT4-, OKT5-subset and with suppressor cells) and with OKM 1, 2 (specific for monocytic and myelocytic cells) was measured on over 90 percent of the leukemia cells, respectively. We suggest that the hybrid cell phenotype (lympho-monocytic) which became clonally expanded in this patient may be representative for a normal cell counterpart exhibiting both NK and ADCC activity. (no Refs)

24. FC RECEPTOR (FCR) HETEROGENEITY IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) (MEETING ABSTRACT).

Ravindranath Y, Kaplan J, Schultz G
Children's Hospital of Michigan, Detroit, MI
Pediatr Res; 15(4,Part2):585 1981

We have previously shown that null cell ALL (sheep RBC receptor -ve, surface immunoglobulin -vel to be either human B lymphocyte antigen (HBLA) positive or human T lymphocyte antigen (HTLA) positive. Thirty children with HBLA +ve null cell ALL were further studied for the presence or absence of FcR on the leukemic blast cells by rosette formation with ex RBC sensitized with IgG or IgM rabbit antibody. Twenty-two were FcR -ve. Eight were IgM FcR +ve. None had IgG FcR. Of the various poor prognostic parameters examined the two groups differed only with respect to sex distribution. Males were predominantly FcR -ve and an unexpectedly higher number of females were FcR +ve, P equals 0.048. The complete remission rate at 3 yr did not differ significantly in the two groups. The data suggest that within the HBLA +ve null cell leukemia heterogeneity exists with respect to FcR positivity. FcR- phenotype is more common. The FcR + group had an unexpectedly higher number of females. The clinical significance of this heterogeneity is still to be determined. (no Refs)

25. MALIGNANT MONOBLASTS CAN FUNCTION AS EFFECTOR CELLS IN NATURAL KILLER CELL AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY ASSAYS (MEETING ABSTRACT).

Hokland P, Ellegaard J
University Department of Medicine and Haematology, Aarhus, 8000, Denmark
Immunobiol; 159(1/2):136 1981

Pure acute monoblastic leukemia was diagnosed in bone marrow aspirations from two male patients by the use of conventional cytochemical methods as well as multiple immunological techniques including the detection of acute lymphoblastic leukemia (ALL) antigens and the terminal transferase enzyme. These malignant cells were subsequently found to be potent effector cells in the natural killer (NK) and antibody-dependent cellular cytotoxicity (ADCC) assays. Whereas no modulation was found in ADCC partially purified alpha-interferon was found to exert an enhancing effect on the NK activity. These findings will be discussed in the light of our present knowledge concerning the assignment of NK cells to lymphoid or myeloid cell lineages. (no Refs)

26. SUPPRESSION OF LYMPHOCYTE PROLIFERATIVE AND CYTOTOXIC RESPONSES BY HUMAN TUMOR-ASSOCIATED IMMUNOREGULATORY FACTORS (MEETING ABSTRACT).

Roth JA, Grimm EA, Gupta RK, Sugarbaker RA, Ames R
National Cancer Institute, Bethesda, MD, 20205
Immunobiol; 159(1/2):190 1981

Immunoregulatory factors (IRF) that suppress normal human lymphocyte function can be extracted from a variety of fresh human tumors. Three M potassium chloride extracts of 18 of 29 fresh human tumor specimens, including sarcomas, melanomas, and lung carcinomas, markedly inhibited 3H-leucine and 3H-thymidine incorporation by lymphocytes in response to mitogens (phytohemagglutinin, concanavalin-A, pokeweed mitogen) and pooled mitomycin-C treated allogeneic lymphocytes. Induction of human allospecific cell-mediated cytotoxicity was also inhibited. Human IRF inhibited murine one way mixed lymphocyte culture responses and induction of allogenic cell-mediated cytotoxicity. Extracts of human normal and fetal tissues were not inhibitory. IRF could be extracted from cultured tumor cells and from concentrated spent culture media from a melanoma cell-line grown in chemically-defined serum-free media demonstrating IRF is a tumor product. Although IRF were extracted from 3 histologically distinct tumors, the extracts had several commmon characteristics. Preincubation with IRF followed by washing prevented inhibition. Inhibition was greatest when IRF were added immediately to cultures. IRF were heat stable and resisted inactivation by trypsin, chymotrypsin, protease, and papain. Inhibitory activity was removed from extracts by lentillectin affinity chromatography and recovered by elution with 3% alpha-methyl mannoside indicating the active moiety contained a carbohydrate. IRF were further purified by sequential Sephadex G-200 and G-75 gel filtration. Inhibitory activity was present in peaks of two molecular sizes: 45,000 to 78,000 and greater than 106,000 daltons. Treatment with 2-mercapto-ethanol eliminated these peaks on subsequent gel filtration and produced 5 smaller peaks which were not inhibitory. Our results demonstrate that factors produced by human tumors suppress a variety of cell-mediated immune responses. Factors from histologically different tumors possess very similar biochemical and immunobiological characteristics. (no Refs)

27. CYTOCHEMISTRY AND MEMBRANE MARKERS IN ACUTE LYMPHATIC LEUKAEMIA (ALL).

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Scand J Haematol; 26(4):311-320 1981

One hundred thirty-six patients suffering from ALL were subdivided into 5 subtypes (C-ALL, C/T-ALL, pre-T-ALL, B-ALL) according to rosetting tests and using specific antisera directed against membrane antigens. In addition, leukemic blasts of all patients were investigated according to morphological and cytochemical criteria. In APh and ANAE, indices and the percentages of cases showing a granular staining pattern were high in pre-T- and in T-ALL, but low in C/T- and in C-ALL. PAS-stai ning, conversely, was more pronounced in C/T- and C-ALL. APh proved to be more discriminative for recognition of the T- and Pre-T-ALL subgroups than ANAE, but ANAE-cytochemistry may be useful to detect contaminating normal T-lymphocytes in ALL. Receptors for C3 were more frequent in C- and in T-ALL than in C/T- and in pre-T-ALL, receptors for Fc were distributed equally among all subtypes. Positivity of C3-and Fc-receptors was not correlated with cytochemical results. Morphological criteria were not sufficient for subclassification of ALL; the combination of APh- and PAS-staining, however, is valuable to differentiate between C-subgroups and T-subgroups. (Author abstract) (36 Refs)

28. THE ACCURACY OF IDENTIFYING T CELL LEUKEMIA USING E ROSETTING OF BONE MARROW LYMPHOBLASTS (MEETING ABSTRACT).

Pincus JK, Falletta JM, Metzgar R, Pullen J, Crist W, Humphrey GB, Boyette J, Van Eys J
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Pediatr Res; 15(4,Part2):602 1981

The identification of sheep erythrocyte rosettes (ER) formed by acute lymphocytic leukemia (ALL) cell (blasts), at 4C has permitted investigators to distinquish patients with presumed T cell ALL from those with non-T ALL. The identification of T antigen (T-ag) on the blasts, detected by monoclonal or carefully absorbed xenoantisera, now permits an analysis of how accurately ER positivity distinguishes T from non T ALL. Bone marrow blasts from 354 pediatric patients with untreated ALL were examined for ER and T-ag. Using the reference point of greater than or equal to 10% (20%) ER (+) blasts to define T cell disease would have led to the incorrect judgement that 37(10) T-ag (-) patients had T cell ALL, a 60% (16%) excess, while 19 (26) T-ag (+) patients would have been excluded, a 31% (42%) deficit. This degree of error in subclassification could substantially affect the results of descriptive studies on therapeutic trials in T cell leukemia, indicating the need for careful T-ag detection in classifying ALL. (no Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

29. SIGNIFICANCE OF SIALIC ACID AND CARCINOEMBRYONIC ANTIGEN AS MONITORS OF TUMOR BURDEN AMONG PATIENTS WITH CARCINOMA OF THE OVARY.

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Advanced Therapeutics Dept., Cancer Control Agency British Columbia, Vancouver, British Columbia, Canada
Surg Gynecol Obstet; 153(2):209-213 1981

Serum sialic acid may serve as a valuable tumor marker for a variety of malignant neoplasms. To evaluate the clinical significance in carcinoma of the ovary, both sialic acid and carcinoembryonic antigen were measured in 69 patients with carcinoma of the ovary. Eligible patients all had assessable tumor burden: in group I, 11 patients had no evidence of disease 4 to 8 wk after surgical assessment; in grou p II, 21 patients had no tumor more than 2 cm in diameter; and in group III, 37 patients had advanced disease. While intergroup comparisons for carcinoembryonic antigen showed no differences between tumor burden groups, sialic acid was significantly related to tumor burden by the same pairwise statistical analysis. Of the 58 patients with demonstrable tumor burden, 36 demonstrated sialic acid elevations as compared with 13 elevations for carcinoembryonic antigen. During serial follow-up study, there were 41 episodes of objective change in tumor burden. There were concordant changes in sialic acid in 95%, and in 85%, these were considered significant. For patients responding to treatment, reduction in tumor burden was relatively rapid, providing no effective lead time between change in sialic acid and other evidence of clinical improvement. Of the progressing pa-

tients with significant changes in sialic acid, 85% demonstrated a lead time of 1 to 21 wk. Although suggested by others as a clinical marker, in this study, carcinoembryonic antigen did not correlate with tumor burden. However, we did find a significant correlation between sialic acid and tumor burden, and the results of serial studies suggested that this may be clinically valuable in guiding patient management. (Author abstract) (7 Refs)

30. CLINICAL EVALUATION OF HUMAN CHORIONIC GONADOTROPIN (HCG), ALPHA-FETOPROTEIN (AFP), PROSTATIC SERUM ACID PHOSPHATASE (PSAP), CARCINOEMBRYONIC ANTIGEN (CEA) AND BETA-2-MICROGLOBULIN (B2MG) AS TUMOR MARKERS IN UROGENITAL MALIGNANCIES.

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Dept. Urology, Faculty Medicine, Kyoto Univ., Kyoto, Japan

Hinyokika Kiyo; 27(3):269-278 1981

Serum hCG and AFP for testicular germ cell tumors, prostatic serum acid phosphatase (PSAP) for prostatic carcinoma, and serum CEA and B2MG for urogenital malignancies were measured by radioimmunoassay (RIA) techniques. A. Specific tumor marker: 1) hCG and AFP: AFP was detected in embryonal carcinoma (EC), infantile EC and teratocarcinoma (TC). AFP and/or hCG was detected in the mixed type of tumor consisting of EC, TC and choriocarcinoma. This was dependent on the major histological component of the tumor. Even in the pure seminoma, elevation of hCG was noted in 4 out of 17 cases, followed by normalization after orchiectomy. Alteration of AFP and hCG well demonstrated an effect of treatment and clinical courses. Reelevation of the markers revealed an advance of clinical staging and recurrence of the tumor. 2) PSAP: Serum levels of PSAP by RIA method correlated well with those by enzyme method but showed fewer pseudonegative values. Elevation of PSAP gave a clue to the initial diagnosis and to earlier detection of recurrence of prostatic carcinoma. B. Nonspecific tumor marker: 1) B2MG: Elevation of B2MG was seen in patients with a dvanced stage of urogenital malignancies. Such a rate of elevation was 62.5% in testicular carcinoma, 55.6% in renal cell carcinoma, 48.1% in bladder carcinoma, 45.5% in pelvic and ureteral tumors and 22.2% in prostatic carcinoma. B2MG increased in 46.9% of advanced urogenital cancers as a whole. 2) CEA: CEA was also elevated in the advanced stage of urogenital cancers, although its percentage was less than that in B2MG. Elevation of CEA was detected in 44.4% of prostatic carcinomas, 37.0% of bladder carcinomas, 36.4% of pelvic and ureteral tumors and 22.2% of renal cell carcinomas. No testicular carcinomas revealed an abnormal CEA value. 3) Combination of B2MG and/or CEA did not raise positive rates of the markers in each of the urogenital cancers. However, when these patients were divided into three groups such as 'alive' with disease and 'dead', according to the survival states, elevation of B2MG or B2MG and CEA was seen in patients in whom tumorous lesions were not eliminated or recurrence was noticed, indicating a poor prognosis. In conclusion, to estimate AFP and hCG or PSAP, as a specific tumor marker, and B2MG and/or CEA, as a nonspecific tumor marker, is a useful adjunct to detect clinical courses and to predict prognosis of urogenital malignancies. (28 Refs) (In JPN)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

31. EVALUATION OF A RADIOIMMUNOASSAY MEASURING ACIDIC GLYCOPROTEIN LEVELS IN SERA OF BREAST CANCER PATIENTS (MEETING ABSTRACT).

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4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

A radioimmunoassay (RIA) was developed at Cedars-Sinai Medical Center using an acidic glycoprotein antigen isolated from neural tissue. The antigen has a subunit mol wt of 40,000+/-3,000. This assay was applied to a group of breast cancer patients (180) to evaluate its diagnostic potential. The normal values were 52.2+/-11.9 arbitrary units. Normal smokers exhibited av values which were 15% higher. Patients with primary infiltrating ductal carcinoma prior to treatment had a mean value of 59.7 with 6% positive. Patients with primary carcinoma and distant metastases prior to treatment had a mean value of 73.7 with 53% positive. Of the patients with distant metastases who have failed treatment, 41% were positive with a mean value of 77.7. The assay was positive for 11.9% of patients who were clinically identified with no evidence of disease. Patients with non-malignant conditions had a mean value in the normal value. Of the 45 patients who were carcinoembryonic antigen (CEA) positive, 11 (24.5%) were also positive in our RIA. Of the 23 patients who were CEA negative, 4 (17%) were positive in this assay. The potential usefulness of this RIA lies in monitoring the efficiency of various therapeutic modalities and in its inclusion in a panel of markers which would predict a gradual breakdown in three-dimensional tissue integrity. (no Refs)

32. SERUM ANIONIC PROTEINS AND NEOPLASM EXTENSION (MEETING ABSTRACT).

Cunietti E, Palma R, Gandini MC, Viola P, Gandini R, Fasoli A

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Tumori; 67(2,SupplA):198 1981

Soluble perchloric proteins (SPP) and N-acetylneuraminic acid (NANA) were determined in the supernatant of perchloric acid treated serum from 40 healthy volunteers (av age 46 yr), 69 patients with non-neoplastic diseases (av 56 yr) and 149 tumor patients (av 61 yr). The SPP and NANA levels in healthy volunteers are 0.65 +/-0.03 ESM mg/ml and 78.4 +/-4.24 ug/ml, in accordance with the literature. In subjects with non-neoplastic disease the SPP av is 0.75 +/-0.04 mg/ml and the av NANA is 133.3 +/-10.06 ug/ml, both significantly higher than in normal subjects (P less than 0.001). In the series of tumor patients the subgroup without current signs of tumor (62 operated patients, under observation or in prophylactic chemotherapy) has av SPP and NANA values of 0.66 +/-0.02 mg/ml and 81.0 +/-3.98 ug, quite close to the av for the normal subjects. In 25 cases of neoplasm with locoregional spread the SPP av 1.0 +/-0.09 mg/ml and the NANA 147 +/-16.01; significantly higher than the preceeding group (P less than 0.001). In the group of 52 patients with metastasis the av SPP is 1.05 +/-0.07 mg/ml and the av NANA 184.7 +/-19.03 ug/ml, not significantly different from the preceeding group, but significantly higher than the control group and the 1st neoplasm subgroup. The NANA was closely related to the SPP in the overall case series (r 0.78 P less than 0.001). From

the data obtained it seems that determination of the SPP and NANA can be useful in evaluating the course of neoplasms while not demonstrating a specificity of practical value in the diagnosis of neoplasms. (no Refs) (In ITA)

33. ONCOFETAL ANTIGEN-I: DISTRIBUTION IN HUMAN TUMORS.

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JNCI; 67(3):557-562 1981

Oncofetal antigen-l (OFA-l) is a human tumor-associated fetal antigen that cross-reacts with fetal brain. The biological distribution of this antigen was studied in a variety of histologic types of human tumors and normal tissues. A total of 170 human tumors and 89 normal tissues obtained from biopsied and autopsied specimens were tested by immune adherence absorption assay. The antigen was most prevalent in malignant melanomas (82%); next in order of incidence were lung carcinomas (71%), sarcomas (61%), brain tumors (58%), and breast carcinomas (53%). However, OFA-l was found in only 15% of gastrointes tinal tumors. The four hepatoma specimens tested were negative for OFA-l. OFA-l was also present in metastases and normal-appearing tissues of patients with OFA-l positive tumors but was not found in normal tissues from noncancer patients. These studies demonstrated that OFA-l is widely distributed among human tumors. It appears to be more prevalent in tumors of ectodermal and mesodermal origin. (Author abstract) (34 Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

34. THE G-IX ANTIGEN OF MURINE LEUKEMIA VIRUS: AN ANALYSIS WITH MONOCLONAL ANTIBODIES.

Pierotti M, DeLeo AB, Pinter A, O'Donnell PV, Hammerling U, Fleissner E
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Virology; 112(2):450-460 1981

The GIX antigen of murine retrovirus gp70 is a marker for virus replication in various cell types, as well as for T-cell differentiation and leukemogenesis in particular mouse strains. The serological definition of GIX depends on the cytotoxicity of a particular rat antiserum for thymocytes from strain 129 mice. We have found that two rat monoclonal antibodies, elicited by immunization with AKR ecotropic virus or AKR leukemia cells, co-type closely with GIX in several assay systems. Like GIX, the epitopes identified by the monoclonal antibodies are amplified on thymocytes during leukemogenisis in AKR mice. These antibodies are cytotoxic for GIX+ leukemia cells and for fibroblasts infected with GIX+ viral serotypes. Though absorbed by GIX+ thymocytes of various strains, the antibodies are not cytotoxic for these cells. We ascribe the latter result to lower representation of antigenic sites on normal thymocytes, and postulate that more than one epitope may participate in classical GIX-mediated cytotoxicity. The monoclonal antibodies do not react with viral env products synthesized in the presence of the inhibitor of glycosylation, tunicamycin. Reactivity with the antibodies appears to require a stable configurational change in the env precursor protein coinciding with glycosylation, rather than direct participation of carbohydrate in the antigenic site. Thus subsequent enzymatic removal of carbohydrate chains in vitro does not alter reactivity with the antibodies. (Author abstract) (42 Refs)

35. INDUCTION OF SEVERAL NEW ANTIGENS, INCLUDING A T CELL-ASSOCIATED ANTIGEN, FOLLOWING CONVERSION OF THE EBV-NEGATIVE B CELL LINE RAMOS TO EHRB-RAMOS BY EPSTEIN-BARR VIRUS.

Rosenthal KS, Shuman H, Strominger JL
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J Immunol; 127(2):746-754 1981

Heteroantisera prepared against EHRB-RAMOS cells and then absorbed extensively with the syngeneic EBV-negative cell line RAMOS recognized a membrane antigen present on EHRB-RAMOS but not on RAMOS cells. The binding of the sera, anti-EHRB, was measured by several immunologic techniques t hat detect cell surface molecules, including cytotoxicity, immunofluorescence, and the 125I-staph protein A assay. Triton X-100 extracts of plasma membranes prepared from EHRB-RAMOS competed for the binding of anti-EHRB on EHRB-RAMOS, as measured by the staph protein A assay, whereas extracts of RAMOS membranes did not. The anti-EHRB sera also recognized the EHRA-RAMOS cell line, but binding of anti-EHRB to other EBV-converted RAMOS lines--African Burkitt lymphoma lines, newly established and well established lymphoblastoid cell lines, and EBV producer cell lines--was undetectable. The anti-EHRB sera recognized 4 T cell lines established from T cell leukemias, including CEM, HSB, YT4E, and MOLT 4. In addition, an anti-CEM serum, prepared in this laboratory, recognized the EHRB-RAMOS cells. Absorption of the serum with peripheral blood lymphocytes removed the activity of anti-EHRB to both the T cell lines and to EHRB-RAMOS, as detected by immunofluorescence using the fluorescence-activated cell sorter. The EHRB-RAMOS cells still retained B cell characteristics, since they expressed p29, 34, an antigen found on normal peripheral B cells, and did not rosette with sheep RBC. The anti-EHRB sera and anti-CEM sera were further characterized by radioimmunoprecipitation of 35S-methionine-labeled proteins of EHRB-RAMOS, RAMOS, YT4E, CEM, and HSB. Anti-EHRB recognized polypeptides of 16, 32, and 35 x 10(3) daltons on EHRB-RAMOS and 85 x 10(3) daltons on EHRB-RAMOS, CEM, HSB, and YT4E. Anti-CEM recognized polypeptides of 95 to 130 x 10(3) daltons expressed on the T cells and EHRB-RAMOS. These polypeptides were absent from or expressed to a much less extent on RAMOS. Thus conversion of RAMOS by EBV to the EHRB-RAMOS B cell line was associated with the appearance of several different antigens, some of which were also present on 4 T cell lines and on peripheral blood lymphocytes (as evidenced by absorption). (Author abstract) (42 Refs)

36. IMMUNOREGULATORY CHANGES INDUCED BY TOTAL LYMPHOID IRRADIATION (TLD). I. APPEARANCE OF A POPULATION OF CELLS BEARING THE THYMUS LEUKEMIA (TL) SURFACE ANTIGEN IN THE LYMPH NODES AND SPLEEN.

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J Immunol; 127(3):1085-1089 1981

BALB/c mice were treated with total lymphoid irradiation (TLI; 3,400 rads) or single-dose, whole-body irradiation (WBI; 550 rads), and the lymph nodes and spleen were assayed for the level of H-2, Ia, Thy-1.2, Lyt-1.2, Lyt-2.2,3.2 and TL-bearing cells by an in vitro cytotoxicity assay. The level of cells bearing all these markers, except for TL, was similar to that observed in normal unirradiated mice. The level of TL+ cells was increased 10-to 20-fold in the TLI-treated mice as compared to WBI-treated mice or normals. The increased number of TL+ cells persisted for at least 200 days after radiotherapy, and was not dependent upon irradiation of the thymus. However, thymectomy before TLI prevented the subsequent development of peripheral TL+ cells. The findings suggest that this abnormal subpopulation of T cells develops as a result of changes in the peripheral lymphoid tissue microenvironment induced by TLI. (Author abstract) (21 Refs)

37. SERIAL TRANSPLANTATION OF A HUMAN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA LINE INTO NUDE MICE.

Miyoshi I, Ota T, Hiraki S, Sumadi M, Tanaka T, Kimura I
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Br J Cancer; 44(1):124-126 1981

The serial transplantation of an ascites form of human T-cell acute lymphoblastic leukemia (ALL) into male and female athymic nude mice with a BALB/c genetic background is described. Of a total of 39 nude mice transplanted over a period of 15 mo, 29 showed a progressive growth of tumors, killing the hosts 29-62 days after implantation. There were multiple tumor nodules involving the intra-abdominal organs and retroperitoneums, with 0.5-6 ml of hemorrhagic ascites. Many of the tumor-bearing mice showed slight enlargement of the mediastinal lymph nodes and spleen but peripheral lymph nodes were not appreciably enlarged. Pleural effusion was also seen in a few animals. Histologically, leukemic infiltration was usually found in the liver, spleen, kidneys, lungs, and lymph nodes. In addition, a single mouse showed leukemic infiltration into the choroid of one eye. Hepatic infiltrates were diffuse in the portal and sinusoidal spaces. The ascites contained 1-4 x 10(8) tumor cells/ml. The WBC count of tumor-bearing mice was 11,000-35,000/cubic mm. Of the ascites tumor cells examined, 80-90% formed spontaneous rosettes with sheep erythrocytes. The results indicated that cells from a continuous cultures line of human T-cell ALL (TALL-1) can be serially transplanted into BALB/c nude mice. (10 Refs)

38. DEMONSTRATION OF SUPPRESSOR CELLS IN LYMPH NODES OF MICE BEARING A SYNGENEIC NON-METASTASIZING (EB) LYMPHOMA (MEETING ABSTRACT).

Shantz G, Knoop H, Umiel T
Department of Biology, Institute of Immunology, University of Heidelberg, Heidelberg, W. Germany
Immunobiol; 159(1/2):193 1981

Our previous studies in a syngeneic tumor model showed that the lymph node draining either a metastasizing (ESb) or non-metastasizing (Eb) tumor contained cells which could directly kill 75 Se-Me labelled tumor cells in a 20 hr Se release assay for primary cell-mediated immunity. These cytotoxic lymph node cells: (1) were highly specific, showing that cells from the draining lymph node recognized distinct non-cross-reacting antigens present on ESb and Eb and (2) were present when the tumor had an optimal size of 0.30-0.35 cm for ESb and 0.35-0.75 cm for Eb. Our recent studies with the Eb tumor showed that th is draining lymph node cytotoxicity was due to T cells and that these could be detected 13 days after im injection of tumor cells. We then looked for cytotoxic cells in the lymph nodes of animals in later stages of tumor development, 27 days after injection of tumor cells when the tumor was 4 x as large (1.83 cm) as it was at day 13 (0.43 cm). We found the following results: (1) the draining lymph node was buried within the tumor and was thus not accessible for cytotoxicity testing; (2) the non-draining lymph nodes (from the nontumor side of the animal) contained no cytotoxic cells; (3) however, cell mixture experiments showed that non-draining lymph nodes cells from animals bearing large 27 day old tumors inhibited the draining lymph node cytotoxicity from animals bearing small 13 day old tumors; (4) similarly, cells from the thymus of animals bearing large 27 day old tumors were also inhibitory, but to a lesser extent than cells from the non-draining lymph nodes. These results are interpreted in the following way: when a non-metastatic tumor is small, cytotoxic T cells are present in the draining lymph node, whereas when it grows larger, cells of a suppressive nature appear in the non-draining lymph nodes and the thymus. The exact nature and specificity of these suppressor cells remains to be identified. The presence of such suppressor cell in vivo may be connected with the observation that large Eb tumors can sometimes shift to their metastasizing variant in vivo. (no Refs)

39. SPONTANEOUS INTERLEUKIN 2(IL-2) PRODUCTION BY HUMAN LEUKEMIC CELLS IN TISSUE CULTURE (MEETING ABSTRACT).

Wernet P, Borowitz A, Ziegler A, Kramer PH, Pawelec G
Department of Medicine, Tubingen University, D-7400 Tubingen, W. Germany
Immunobiol; 159(1/2):203 1981

Since IL-2 is conventionally from WBC activated with T cell mitogens, it was considered possible that pathologically active leukemic T cells might also be producing IL-2. Thus five established T cell lines as well as six clearly diagnosed T cell leukemias with different surface phenotypes - determined in indirect immunofluorescence with greater than 30 monoclonal antibodies - were screened for IL-2 production. These cells were cultured for short periods of time (6-72 hr) in RPMI 1640 medium containing 20% fetal calf serum and 10% human serum, and for some experiments supplemented with 1% phytohemagglutinin (PHA) or 10 ng/ml of the phorbol diester 12-O-tetradecanoyl-phorbol-13 acetate (TPA), or both. Only two out of five variants of JURKAT produced detectable amounts of IL-2, as measured in a standard thymidine incorporation microassay on cloned human and murine T cell lines; and two produced IL-2 without stimulation by mitogens. In addition, one of the active JURKAT variants was cloned by limiting dilution, and a clone derived which retained high spontaneous IL-2 production. Although exposure of active JURKAT lines to PHA or/ and TPA produced a lymphokine superior to the uninduced IL-2 source in he 24 hr thymidine incorporation assay, suprisingly the reverse was observed when the IL-2 sources were compared for their actual ability to sustain long term growth of alloactivated cloned T cell lines for six days or longer. The two IL-2 producing JURKAT variants differed in

three surface markers from the three non-IL-2 producing JURKAT variants. Of the six T cell leukemias two were found to produce IL-2 spontaneously as well as after PHA or/TPA induction. These two-both proliferating only slowly-were a Sezary cell type which produced only moderate amounts of IL-2 and a chronic lymphatic leukemia of T cell type which in contrast produced exceptionally high IL-2 activity, surpassing a conventionally prepared reference IL-2 source. (1 Ref)

40. CHARACTERISATION OF HODGKIN CELLS (MEETING ABSTRACT).

Diehl V, Kirchner HH, Stein H, Fonatsch C, Schaadt M
Inst. f. Pathologie, Universitat Kiel, Hannover, W. Germany
Immunobiol; 159(1/2):186 1981

To overcome the difficulties to analyze freshly isolated Hodgkin-(H) and Sternberg-Reed (SR) cells we established four in vitro cell lines from three patients with histologically proven Hodgkin's disease (L 428, L 439 from pleural effusions of different patients, L 538, L 540 from bone marrow and peripheral blood of the same patients). The neoplastic nature of the culture cells is indicated by the demonstration of several structural and numerical chromosome abnormalities associated with a monoclonal pattern of marker chromosomes. Heterotransplantion in nude mice resulted in tumor growth with all cell lines after intracranial inoculation, with the L 428 after sc transplantation embedded in a plasma clot and only with the L 540 after im inoculation. Ia-like antigens, acid phosphatase and acid esterase were found to be present in the culture cells. The L 428 and L 439 showed also receptors for human T-cells. All cell lines lacked EBV-specific antigens, surface or cytoplasmic Ig, HTLA, receptors for C3b, C3d, IgG-Fc, mouse E or sheep E and were devoid of lysozyme, peroxidase and chloracetate esterase. These features do not correspond to that of B-cells, T-cells, myeloid cells, monocytes or macrophages. The morphology and the marker pattern of the culture cells, however, is identical with that of freshly obtained H- and SR cells, except for the lack of CIg in the in vitro cells. Antisera were raised in rabbits against the L 428 cells. After absorption with various lymphoid and myeloid cells the antiserum reacted only with L428 cells and the H and SR-cells in biopsies from 11 cases of Hodgkin's disease. These findings suggest that the L 428, L 439 and L 538/540 cell lines are indeed derived from H- and SR-cells and are helpful to define the origin and specific membrane structures of the malignant cells in Hodgkin's disease. (no Refs)

41. NEW PLACENTAL PROTEINS AND THEIR POTENTIAL DIAGNOSTIC SIGNIFICANCE AS TUMOR MARKERS.

Bohn H, Luben G
Res. Labs., Behringwerke AG, D-3550 Marburg, W. Germany
Oncodev Biol Med; 2(3):141-153 1981

Several pregnancy proteins and placental proteins were reviewed. Five newly-discovered soluble placental proteins, PP8, PP9, PP10, PP11, and PP12, . were isolated from aqueous extracts of human term placentae. PP8, PP10, PP11, and PP12 were alpha-globulins. PP9 was a beta-globulin. The mol wt ranged from 25,200 to 65,000 daltons. Carbohydrate content ranged from 3.9 to 6.6 %. The biological function of the proteins was unknown. PP12 was identical or similar to the chorionic alpha-1-microglobulin. PP8 and PP9 occurred in all tissues, while PP10, PP11, and PP12 appeared to be specific to the placenta. PP10, PP11, and PP12 were found in tumor tissue. Data suggest that these proteins may be useful as tumor markers. (23 Refs)

42. A NOVEL CELLULAR RETINOID-BINDING PROTEIN, F-TYPE, IN HEPATOCELLULAR CARCINOMA.

Muto Y, Omori M
First Dept. Internal Medicine, Gifu Univ. Sch. Medicine, Gifu City, Japan
Ann NY Acad Sci; 359:91-103 1981

The occurrence of the specific cellular retinol-binding protein previously identified in the fish-eye cytosol [CRBP(F)] was studied. [3H]-retinol binding assay showed the presence of CRBP(F) in 7/10 surgery specimens of hepatocellular carcinoma; CRBP(F) was detected in 4/5 patients with alpha-fetoprotein level of less than 200 nanog/ml. Vitamin A content in the tumor tissue was significantly lower than in the surrounding noncancerous tissue. The presence of CRBP(F) was also detected in the human fetal liver, in regenerating rat liver, and in hyperplastic liver nodules induced in rats by 2-acetylaminofluorene. CRBP(F) was found to be distinctly different from cellular retinoic acid-binding protein with respect to isoelectric point and relative electrophoretic mobility. These findings indicate that CRBP(F) can be considered as a novel onco-fetal protein, and that it is possible to prevent the experimental carcinogenesis by targeting retinoids to the hyperplastic nodules before hepatocellular carcinoma is established. (35 Refs)

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. CARCINOEMBRYONIC ANTIGEN AND PROGNOSIS AFTER RADICAL SURGERY FOR LUNG CANCER: IMMUNOCYTOCHEMICAL LOCALIZATION AND SERUM LEVELS.

Ford CH, Stokes HJ, Newman CE
Surgical Immunology Unit, Clinical Oncology, Univ. Birmingham, Queen Elizabeth Hosp., Edgbaston, Birmingham B15 2TH, England
Br J Cancer; 44(2):145-153 1981

Eight-two percent of tumor sections from 105 patients with lung cancer showed positive immunocytochemical localization of an anti-carcinoembryonic antigen (CEA) Ig free of antibody to normal cross-reacting antigen (NCA). The highest incidence was found in adenocarcinomas, and no association between staining and disease stage was found. There was a relationship between positive-staining tumors and preoperative and postoperative serum CEA levels of greater than or equal to 20 ng/ml, but the high incidence of CEA+, less than 20 ng/ml serum patients indicated that immunocytochemical localization was of little value in selecting patients for sequential serum monitoring. Staining for CEA was not prognostic but a preoperative serum CEA level greater than or equal to 20 ng/ml was associated with a poor prognosis in patients undergoing radical surgery for lung cancer ($p = 0.043$). This prognostic effect of CEA was seen mainly in patients whose tumors showed the greatest immunocytochemical localization ($p = 0.017$) and in Stage III patients ($p = 0.04$). (Author abstract) (29 Refs)

2. CARCINOEMBRYONIC ANTIGEN ESTIMATION IN CEREBROSPINAL FLUID IN PATIENTS WITH METASTATIC BREAST CANCER.

Dearnaley DP
Ludwig Inst. for Cancer Res. (London Branch), Royal Marsden Hosp., Sutton, Surrey, England
Oncodev Biol Med; 2(4):305-311 1981

The value of measuring cerebrospinal fluid (CSF) levels of carcinoembryonic antigen (CEA) as a guide in the differential diagnosis of patients with breast cancer and neurologic symptoms was examined in 39 patients with metastatic breast carcinoma (22 of whom had metastases to the CNS) and 13 control patients with various benign neurological disorders. None of the control patients had any detectable CSF CEA. There was no correlation between CEA levels in simultaneously obtained plasma and CSF samples in the patients with metastatic breast cancer. Immunoreactive CSF CEA was found in 13/22 patients with breast cancer metastases involving the CNS and in 4/17 without CNS involvement. A similar range of values of CSF CEA was found in patients with meningeal infiltration, extra-dural spinal metastases, or without CNS involvement, showing that the degree of elevation of CSF CEA is not helpful in determining the site or presence of CNS involvement in patients with metastatic breast cancer. (12 Refs)

3. EVALUATION OF A COMMERCIAL ENZYME IMMUNOASSAY KIT FOR SERUM CARCINOEMBRYONIC ANTIGEN.

Fabricatorian D, Gallagher ND
A. W. Morrow Dept. Gastroenterology, Royal Prince Alfred Hosp., Missenden Rd., Camperdown, NSW 2050, Australia
Ann Clin Biochem; 18(part4):248-251 1981

The Abbott CEA-EIA Diagnostic enzyme immunoassay kit for measuring serum carcinoembryonic antigen (CEA) is evaluated and compared to the Roche-CEA Z-Gel radioimmunoassay kit. incubated with extraction buffer and then centrifuged. The supernatant is placed in tray wells. Plastic beads coated with guinea-pig anti-CEA are added as first antibody. The beads are washed. Goat anti-CEA conjugataed with horse radish peroxidase is then added as the second antibody. The beads are again washed, placed in a buffer and incubated. After the reaction is stopped, absorption is measured at 492 nanometer. Results indicate that the method has good reproducibility and no problem with drift in standard values. The cut-off point for elevated CEA is 2.5 nanog/ml. The method tested eliminates the need for labor-intensive dialysis necessary in the other method. A highly-skilled technician is not needed. The kit appears to be an accurate and cheap alternative to other test kits. (14 Refs)

4. ALPHA FETOPROTEIN DETERMINATIONS IN THE MANAGEMENT OF ENDODERMAL SINUS TUMORS AND MIXED GERM CELL TUMORS OF THE OVARY.

Romero R, Schwartz PE
(c/o Schwartz) Dept. Obstetrics and Gynecology, Yale Univ. Sch. Medicine, 333 Cedar St., P.O. Box 3333, New Haven, CT, 06510
Am J Obstet Gynecol; 141(2):126-131 1981

Serum alpha fetoprotein (AFP) titers determined by radioimmunoassay (RIA) techniques may serve as useful tumor markers in patients with endodermal sinus tumors (EST) or mixed germ cell tumors of the ovary containing EST elements when serum AFP is detectable prior to initiation of combination chemotherapy. A decline in AFP titers to less than 20 ng/ml, followed by any subsequent elevation, is an ominous finding suggestive of recurrent or progressive disease and requires prompt diagnostic evaluation and change in management. AFP assays performed by non-RIA techniques lack sufficient sensitivity to be employed routinely as tumor markers. (Author abstract) (16 Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

5. DIAGNOSTIC VALUE OF PROSTATIC ACID PHOSPHATASE IN PROSTATE CARCINOMA AS DETERMINED BY RADIOASSAY.

Wirth MP, Osterhage HR, Ackerman R
Urologische Klinik und Polyklinik der Universitat, Luitpoldkrankenhaus, Josef-Schneider-Str. 2, 8700 Wurzburg, W. Germany
Aktuel Urol; 12(4):150-153 1981

Serum levels of prostatic acid phosphatase (PAP) were determined in 49 patients. Cases included 35 histologically-confirmed prostate carcinomas, and 9 patients with prostate adenomas as controls. Five patients who had undergone radical prostatovesiculectomy for carcinoma were followed for 2-66

mo after operation. PAP determinations were made using four different radioimmunoassay (RIA) kits and by the standard enzymatic method (p-nitrophenylphosphate). Tumors were classified on the basis of histologic examination following radical prostatectomy and dissection of the pelvic lymph nodes. Raised PAP leveis were found in only one case of stage I tumor. In stages II-IV with node involvement and metastases, RIA found raised PAP levels in 54-83% of the cases, depending on the test system used. Results obtained with one system were not comparable to results from another system. The enzymatic method showed raised PAP levels in 39% of the cases. Stage III tumors without node involvement or metastases showed raised PAP levels in 43-78% of the cases, while the enzymatic method showed 11%. No false positive results were obtained from controls. PAP determinations were of no apparent value in early detection of prostate carcinoma, but the RIA method was found useful for measuring the course of advanced stages of the disease. (8 Refs) (In GER)

6. GAMMA-GLUTAMYLTRANSFERASE, A COMMON MARKER OF HUMAN EPITHELIAL TUMORS?

Fiala S, Trout EC, Teague CA, Fiala ES
Cell Physiology Lab., Veterans Admin. Medical Center, Martinsburg, WV, 25401
Cancer Detect Prev; 3(2):471-485 1981

Having previously established gamma-glutamyltransferase (GGT) as a marker of experimental carcinogenesis in rat liver, we investigated whether human tumors differ from their tissue or origin by showing a higher activity or different localization of this enzyme histochemically. We found such differences in each of the human carcinomas we examined. The presence of GGT activity in carcinomas arising in organs normally containing little (tongue) or no GGT activity (larynx, urinary bladder, and esophagus) clearly distinguished cancerous from normal epithelium. In the breast, colon and prostate, GGT activity was normally present in a defined anatomical distribution bordering luminal surfaces. Carcinomas arising from these tissues showed a loss of the normal pattern of activity and contained cells with almost homogeneous GGT activity in the cytoplasm. Such differences clearly distinguished carcinomatous from normal epithelium in these organs. The increased GGT activity observed in all nine carcinomas arising from seven different organs suggests that GGT may be a common marker of human epithelial tumors and staining for GGT may become a useful tool in the detection of human epithelial neoplasms. (Author abstract) (18 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

7. IMPROVED HUMAN CHORIONIC GONADOTROPIN DETECTION WITH CARBOXYL-TERMINAL RADIOIMMUNOASSAY OF THE BETA SUBUNIT ON CONCENTRATED 24-HOUR URINE IN PATIENTS WITH TESTICULAR CANCER.

Javadpour N, Chen HC
Surgery Branch, NCI, NIH, Bethesda, MD, 21205
J Urol; 126(2):175-178 1981

The value of measuring serum levels of human chorionic gonadotropin in detecting and monitoring testicular cancer has been demonstrated convincingly. In this study the human chorionic gonadotropin was extracted by the kaolin-acetone procedure from 24-hr urine specimens and the total vol of the extract was adjusted to 15 ml. With a highly specific immunoassay system (H93) that recognizes the unique carboxyl-terminal peptide of human chorionic gonadotropin beta subunit (residue numbers 123 to 145) as descri bed previously, the urinary human chorionic gonadotropin was measured serially in 32 specimens of 15 patients with initially human chorionic gonadotropin-producing testicular tumors. These 15 patients had simultaneous measurements of serum human chorionic gonadotropin using an antiserum against the beta subunit (Sb6) and urinary human chorionic gonadotropin concentrates using H93 radioimmunoassay. The initial serum hormone levels of these 15 patients were elevated and returned to normal after therapy. However, despite this occurrence the urinary hormone levels also were elevated. The initial five patients with elevated urinary but normal serum human chorionic gonadotropin levels had recurrence. The use of this highly specific radioimmunoassay in measuring urinary human chorionic gonadotropin coupled with effective chemotherapeutic agents has been valuable in selecting patients in whom further therapy is warranted despite normal serum human chorionic gonadotropin and clinically undetectable tumor. (Author abstract) (9 Refs)

8. INFLUENCE OF ESTROGEN RECEPTOR STATUS ON RESPONSE TO COMBINATION CHEMOTHERAPY FOR RECURRENT BREAST CANCER.

Mortimer J, Reimer R, Greenstreet R, Groppe C, Bukowski R
Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH, 44106
Cancer Treat Rep; 65(9):763-766 1981

To determine the influence of cytoplasmic estrogen receptor (ER) status on response to chemotherapy among patients with recurrent breast cancer amenable to biopsy, we studied 65 patients who had ER determinations performed on metastatic lesions. The response to combination chemotherapy and duration of survival were determined in 49 of these patients who received cytotoxic chemotherapy as their sole modality of treatment. Compared to patients with ER levels less than 3 femtomols/mg, patients with an ER concentration greater than or equal to 3 femtomols/mg had a higher response rate (57% vs 21%, p less than 0.05) and a longer survival (35 vs 13 mo, p less than 0.0003). Some of the increased survival of the ER-positive patients was attributable to response to subsequent hormonal manipulations. These differences between ER-positive and ER-negative patients were lessened by redefining ER-positive as greater than or equal to 10 femtomols/mg. Nevertheless, at our institution patients with ER-positive metastatic breast cancer have a higher response rate to chemotherapy and survive longer than their ER-negative counterparts. (Author abstract) (17 Refs)

9. MEASUREMENT OF PROGESTERONE RECEPTORS IN HUMAN BREAST TUMORS: COMPARISON OF VARIOUS METHODS OF ANALYSIS.

Namkung PC, Petra PH
Dept. Lab. Medicine Dept., Univ. Washington Sch. Medicine, Seattle, WA, 98195
J Steroid Biochem; 14(9):851-854 1981

The measurement of estrogen and progesterone receptors in human breast tumors is important to the successful management of the patients. These receptors exist in two macromolecular forms that have different sedimentation coefficients: 4S and 8S. Progesterone receptors were measured simultaneously in freshly prepared tissue cytosols from 10 individual tumors by three methods: the single-saturating dose (SSD) analysis,

the sucrose density gradient method, and the multi-point Scatchard plot analysis. All three methods agreed extremely well for the determination of total (4S + 8S) receptor concentration; there was no loss of receptor-binding activity during the time required for sucrose density gradient analysis. The two macromolecular forms of the receptor appear to have similar if not identical dissociation constants because receptor concentrations calculated by extrapolation of linear Scatchard plots are identical to those obtained from either the summation of 4S and 8S areas of the density gradients or the SSD analysis. All three tested methods can be used in clinical measurements of the progesterone receptor. (14 Refs)

10. ESTROGEN AND PROGESTERONE BINDING PROTEINS IN HUMAN COLORECTAL CANCER. A PRELIMINARY CHARACTERIZATION OF ESTRADIOL RECEPTOR.

Sica V, Contieri E, Nola E, Bova R, Papaleo G, Puca GA
I. Facolta di Medicina e Chirurgia, Istituto di Patologia Generale, Via S. Andrea delle Dame 2, 80138 Napoli, Italia
Tumori; 67(4):307-314 1981

Estradiol receptor (ER) and progesterone receptor (PgR) were assayed in tumors from 20 patients with primary colorectal cancer. Ten of 20 tumors contained high affinity sites for 17beta-estradiol and progesterone. The highest concentration of ER was 56 fmol/mg of protein. The ER dissociation constant ranged from 1.6 x 10(-10) M to 8 x 10(-10) M (mean 4.6 +-2.6). The highest concentration of PgR was 42 fmol/mg of protein. The PgR dissociation constant ranged from 3 x 10(-9) to 9 x 10(-9) M (mean 5.65 +-2.1). Four out of 20 specimens analyzed were from male patients and all resulted negative for both receptors. Sixty percent of ER positive tumors were also PgR positive, whereas only 20% of ER negative were PgR positive. Sucrose gradient centrifugation showed that cytoplasmic ER of colorectal cancer sedimented at 3 S in the absence of protease inhibitors and at 4.5 S in the presence of 1 mM phenylmethylsulphonyl fluoride (PMSF) both in low and in high ionic strength. When chromatographed on Sephadex G-200 almost all ER was quantitatively recovered in the included fractions. Mol wt of ER eluted from Sephadex G-200 ranged from 90,000 to 50,000 daltons. Elution profile and mol wt heterogeneity suggest that, in spite of the presence of PMSF, there is a limited proteolysis of ER. Partially purified colorectal cancer ER did not bind to sepharose-heparin. The isoelectric point of ER was 6.4-6.5. (Author abstract) (35 Refs)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

11. SURFACE PHENOTYPE OF JAPANESE ADULT T-CELL LEUKEMIA CELLS CHARACTERIZED BY MONOCLONAL ANTIBODIES.

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Blood; 58(3):645-647 1981

We studied the surface phenotype and the functional activities of leukemic cells from three patients with Japanese adult T-cell leukemia (ATL) using the panel of OK and anti-Tac monoclonal antibodies, which react with differentiation antigens and define functionally distinct T-cell subsets or activated and terminally differentiated to T cells. The phenotype of ATL cells were determined to be OKT1+T3+T4+T10+T5-T8-OKla1-, although cells from two patients suppressed pokeweed mitogen (PWM) induced normal B-cell differentiation, and cells from all patients lacked helper activity in this system. In addition, after cultivation with PWM, ATL cells from all patients were reactive with anti-Tac monoclonal antibody, and cells from one patient were reactive with OKla1. These findings suggest that ATL cells arise from peripheral mature T-cell subsets and also suggest that the transition of surface phenotype of ATL cells to functionally mature and activated T cells occurs in culture. (Author abstract) (17 Refs)

12. IMMUNOHISTOLOGICAL ANALYSIS OF HODGKIN'S AND STERNBERG-REED CELLS: DETECTION OF A NEW ANTIGEN AND EVIDENCE OF SELECTIVE IGG UPTAKE IN THE ABSENCE OF B CELL, T CELL AND HISTIOCYTIC MARKERS.

Stein H, Gerdes J, Kirchner H, Diehl V, Schaadt M, Bonk A, Steffen T
Inst. Pathology, Univ. Kiel, Hospitalstrasse 42, D-2300 Kiel, W. Germany
J Cancer Res Clin Oncol; 101(1):125-134 1981

The results of studies to clarify the origin and nature of Hodgkin's (H) and Sternberg-Reed (SR) cells are presented. Cytoplasmic IgG (CIgG) was demonstrated by immunostaining in polymorphic astrocytomas, liver cell carcinomas, and other polymorphic neoplasms as well as in H and SR cells. In addition, human IgG was taken up by rat liver cells, but alpha1 antitrypsin was not. These results showed that CIgG cannot be used as a marker for histiocytes. Staining of frozen sections revealed that H and SR cells lacked surface Igs and peripheral T-cell antigen. An antiserum raised against Hodgkin's disease (HD) L 428 cells and absorbed with normal human cells reacted strongly with H and SR cells in frozen sections of HD-affected lymph nodes. In 10 cases, the antiserum stained the surface of the H and SR cells; in 2 cases, it also stained the nucleoli and some chromatin spots. The antiserum did not react with tonsil tissue cells (lymphoid cells, histiocytes, interdigating reticulum cells). It was concluded that the nature of the H and SR cells is still open and that these cells might express antigens that have not yet been detected on normal cel ls. (29 Refs)

13. CYTOGENETIC FINDINGS IN T-ZONE LYMPHOMA.

Godde-Salz E, Schwarze EW, Stein H, Lennert K, Grote W
Dept. Human Genetics, Univ. Kiel, Schwanenweg, D-2300 Kiel, W. Germany
J Cancer Res Clin Oncol; 101(1):81-89 1981

Histologic, immunologic, and cytogenetic findings are reported for five non-Hodgkin's lymphomas that fulfilled the diagnostic criteria of T-zone lymphoma; ie, they contained all the T-region components of lymphoid tissue and also B-region remnants. The patients, aged 64-77 yr, included two women and three men. In 4/5 cases, the lymph node architecture was completely effaced, with the exception of the residual B areas (follicles). The B cells were identified immunologically as the nonneoplastic cells, and the cells that formed rosettes with sheep RBC were found to be the tumor cells. The chromosome analyses revealed abnormal clones as well as normal mitoses in four cases. Structural rearrangements involved chromosomes 1, 2, 3, 4, 14, and Y. Some tumors showed the loss of chromosomes 3, 5, 6, or 13 and some a gain of chromosomes 3 and 9. There was a high frequency of structural and numerical aberrations in chromosome 3, but a low frequency of 14q

markers in one case. The number of patients was too small to determine whether this pattern is specific for the T-zone lymphomas. (21 Refs)

14. IMMUNOLOGIC MARKERS IN THE DIFFERENTIAL DIAGNOSIS OF NON-HODGKIN'S LYMPHOMAS.

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Inst. Pathology, Univ. Kiel, Hospitalstrasse 42, D-2300 Kiel, W. Germany
J Cancer Res Clin Oncol; 101(1):29-42 1981

To improve the Kiel classification of non-Hodgkin's lymphomas (NHLs), 250 NHLs were analyzed for surface markers and enzyme phenotype. B-cell chronic lymphocytic leukemias (CLLs) were characterized by a predominance of complement (C) 3d receptors over C3b receptors, and a high percentage of RBC receptors. Four of five T-cell CLLs showed acid esterase activity but lacked IgG-Fc receptors; the reverse was true of the fifth case. Prolymphocytic leukemias exhibited a high percentage of surface immunoglobulin (SIg)-positive cells and large numbers of C3b and IgG-FC receptor-positive cells. Hairy cell leukemias resembled the prolymphocytic leukemias except for the absence of C3 receptors. T-zone lymphomas contained both T and B cells; the T cells formed rosettes with sheep RBC only at 4 C, and they were identified morphologically as the neoplastic cells. The three types of lymphomas derived from germinal center cells expressed nearly equal numbers of C3b and C3d receptors a low percentage of IgG-Fc receptors. Centrocytic lymphomas, in in contrast to centroblastic-centrocytic (CC) lymphomas, had a high proportion of cells with SIg and C3 receptors and few or no T cells and cells rosetting with mouse RBC. The marker profiles of centrob lastic lymphomas and lymphoplasmacytic subtype of lymphoplasmatic/cytoid lymphomas (IP immnocytomas) resembled that of CC lymphomas. The lymphoplasmacytoid IP immunocytoma subtype had the same markers as B-cell CLLs, but the marker profile of the polymorphic subtype was not similar to any other pattern. Burkitt's lymphoblastic lymphomas were characterized by large amounts of SIg and the absence of all other markers. Four types of T-cell lymphoblastic leukemias were distinguished on the basis of the presence or absence of C3 receptors, sheep RBC receptors, and acid phosphatase, or acid esterase. Of nine immunoblastic lymphomas, eight were the B-cell type (SIg+) and one was the T-cell type (sheep RBC receptors). (19 Refs)

15. INFLUENCES OF AN EXTRACT FROM TUBERCLE BACILLI OF HUMAN TYPE (SSM) ON THE FUNCTION OF HUMAN LYMPHOCYTES: EFFECTS ON POKEWEED MITOGEN-INDUCED IMMUNOGLOBULIN PRODUCTION BY HUMAN LYMPHOCYTES.

Yamakura T, Takahashi K, Shimbo T, Ohtsuka Y
Lab. Immunology, Toho Univ., Japan
Nippon Gan Chiryo Gakkai Shi; 16(3):447-452 1981

SSM human tubercle bacilli extract did not augment in vitro immunoglobulin biosynthesis in normal human lymphocytes in the presence of pokeweed mitogen. However, SSM reversed the depression of lymphocyte function caused by treatment with sera from gastric cancer patients; it also inhibited cancer sera-induced lymphocyte depression. These results were also seen in lymphocytes from healthy subjects with negative purified protein derivative skin tests. (17 Refs) (In JPN)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

16. PRODUCTION OF ALPHA-FETOPROTEIN, NORMAL SERUM PROTEINS, AND HUMAN CHORIONIC GONADOTROPIN IN STOMACH CANCER: HISTOLOGIC AND IMMUNOHISTOCHEMICAL ANALYSES OF 35 CASES.

Kodama T, Kameya T, Hirota T, Shimosato Y, Ohkura H, Mukojima T, Kitaoka H
Pathology Div., Natl. Cancer Center Res. Inst., 5-1-1, Tsukiji, Chuo-ku, Tokyo 104, Japan
Cancer; 48(7):1647-1655 1981

By immunoperoxidase histochemical staining of formalin-fixed paraffin-embedded sections, the production of alpha-fetoprotein (AFP), albumin (ALB), transferrin (TF), alpha-1-antitrypsin (AAT), and human chorionic gonadotropin (HCG) was examined in 35 operatively resected stomach cancers with elevated serum AFP levels (higher than 20 ng/ml as determined by radioimmunoassay). Cells positive for AFP were found in 19 cases (54%). In 29 cases (83%), some tumor cells contained normal serum proteins (ALB, TF, or AAT). All 19 tumors with AFP-positive cells also stained positively for two or three kinds of normal serum proteins. In some cases, AFP and normal serum proteins were localized in the same cells. There were two cases in which metastatic tumors produced AFP, whereas the primary sites did not. In nine cases (26%), HCG was present in tumor cells and HCG- and AFP-positive cells were coexistent in six tumors. Histologic examination of AFP-producing stomach tumors revealed medullary or papillotubular arrangements with marked nuclear atypia and eosinophilic granular or clear cytoplasms containing no glycogen or mucin. Some tumors with medullary patterns resembled liver cell carcinomas. Concordant phenotypic expression of AFP and normal serum protein production appears to be a general feature of AFP-producing tumors such as liver cell carcinoma, yolk sac tumor, and stomach cancer. (Author abstract) (47 Refs)

17. MULTIPLE BIOLOGIC MARKERS IN THE MONITORING OF TREATMENT FOR PATIENTS WITH SMALL CELL CARCINOMA OF THE LUNG: THE USE OF SERIAL LEVELS OF PLASMA CEA AND SERUM CARBOHYDRATES.

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Johns Hopkins Oncology Center, 600 North Wolfe St., Baltimore, MD, 21205
Cancer; 48(7):1633-1642 1981

The monitoring utility of serial patterns of a single marker (carcinoembryonic antigen) level and multiple marker (three carbohydrates-fucose, mannose and galactose) levels in patients with small cell carcinoma of the lung was investigated using a quantitative approach. A serial multiple regression (SMR) model was formulated to assess the disease responses following the 1st to the 10th course of therapy and resulted in the multiple correlations ranging from 0.183 (NS)-0.706 (p less than 0.005) for CEA, and 0.502 (p less than 0.250)-0.760 (p less than 0.025) for three carbohydrates, respectively. The appraisal of these markers utilizing the SMR model points out that: (1) the serial levels of CEA greater than 5.0 ng/ml are significantly correlated with the disease course whereas the serial levels less than 5.0 ng/ml reflect the trend of variation in the disease course, but with less accuracy; and (2) the levels of three car-

bohydrates, any one elevated before and during therapy, are significantly correlated with the disease course. (Author abstract) (31 Refs)

18. SIGNIFICANCE OF SERUM CONCENTRATIONS OF CARCINOEMBRYONIC ANTIGEN, FERRITIN, AND CALCITONIN IN BREAST CANCER.

Bezwoda W, Derman D, Bothwell T, MacPhil P, Levin J, De Moor N
Dept. Medicine, Medical Sch., Hospital St., Johannesburg, S. Africa
Cancer; 48(7):1623-1628 1981

Serum concentrations of carcinoembryonic antigen (CEA), ferritin, and calcitonin were measured in 107 patients with breast cancer, 80 of whom had overt or occult metastatic disease. CEA and ferritin values were statistically higher in those patients with metastases. In contrast, there was no correlation between calcitonin concentrations and the stage of the disease. All 27 subjects with CEA concentrations greater than 80 ug/liter and 32 of 40 with values between 41-80 ug/liter had metastatic disease. Ferritin was a definite but less sensitive discriminator, with metastatic disease present in all nine patients having concentrations greater than 400 ug/liter. Such metastases were invariably hepatic. When the two measurements were used as a combined discriminant, the diagnostic accuracy increased somewhat. All 32 patients with a CEA concentration greater than ug/liter and/or a ferritin concentration greater than 400 ug/liter had metastatic disease; the same was true for 32 of the 42 subjects with CEA concentration between 41-80 ug/liter and/or a ferritin concentration between 200-400 ug/liter. The measurements and prognostic value, both when assessed alone and together, with a median survival from the time of study significantly shorter in those with the highest values. (Author abstract) (23 Refs)

19. MULTIPLE BIOLOGICAL MARKERS AND BREAST CARCINOMA: A PRELIMINARY STUDY IN THE DETECTION OF RECURRENT DISEASE AFTER PRIMARY THERAPY.

Waalkes TP, Abeloff MD, Ettinger DS, Woo KB, Gehrke CW, Mrochek JE
Johns Hopkins Oncology Center, Baltimore, MD, 21205
J Surg Oncol; 18(1):9-19 1981

The use of a selected group of biological markers in breast cancer patients who are disease free but at risk of relapse after mastectomy has potential for detecting recurrent tumor before there is clinical evidence. In this preliminary study, multiple materials were serially analyzed in the body fluids of patients without overt tumor but receiving adjuvant chemotherapy because of positive axillary nodes at surgery. The total frequency of elevated levels was determined and compared for those patients who remained disease free, for those who subsequently relapsed, and for a third group of patients with proven metastases. Frequency of elevation was directly proportional to increasing disease. Although differences in the relative frequency of individual materials were observed, the same trends with increasing tumor burden were found. The results suggest that the serial measurement of biological markers has potential for indicating the presence of occult disease. A nucleus of biological markers to be considered should include carcinoembryonic antigen, urinary hydroxyproline/creatinine ratio for bone lesions, and gamma-glutamyltranspeptidase for liver involvement. (Author abstract) (45 Refs)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

20. 20-YEAR RESEARCH ON THE SUBJECT OF PREGNANCY ASSOCIATED ALPHA2-GLYCOPROTEIN - SIGNIFICANCE OF THE DETERMINATION OF THESE PROTEINS IN CLINICAL STUDY.

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Dtsch Gesundheitswes; 36(28):1193-1199 1981

The range of variation of individual concentrations of pregnancy associated alpha2-glycoprotein (PAG) is not a normal distribution, but a multi-peaked distribution, which presumably is an expression of the genetic background. For this reason it is statistically inadmissible to use mean values for reference purposes. Some physiological or pathological processes have an anabolic influence on the PAG level. They include especially the action of estrogen, tumor growth, immune defects which are possibly manifested humorally, rheumatoid arthritis, hepatitis/diabetes combination. A correlation between predisposition to tumor formation and the PAG level cannot be established in this direct manner. It was determined through family examinations. Decreases in PAG levels after the removal of tumors and early increases in PAG levels in cases of relapse or formation of metastases can be used for case control of tumor risk groups. The other anabolic influences, which are known to date, must be ruled out. The use of PAG determinations as a tumor search test is advisable only when the individual, genetically determined initial values are known. The lowering of the PAG level immediately after the withdrawal of estrogenic contraceptives should be checked during the period without medication. (Author abstract) (66 Refs) (In GER)

21. SERUM THYROGLOBULIN IN THYROID CANCER.

Black EG, Gimlette TM, Maisey MN, Cassoni A, Harmer CL, Oates GD, Hoffenberg R
(c/o Hoffenberg) Dept. Medicine, Univ. Birmingham, Queen Elizabeth Hosp., Edgbaston, Birmingham B15 2TH, England
Lancet; 2(8244):443-445 1981

Serum thyroglobulin (Tg) was measured in 274 patients with differentiated thyroid cancer; 266 had previous thyroidectomy, which had been followed by ablative iodine-131 in 183 cases. Neither the presence nor the titer of anti-Tg antibodies appeared to effect Tg assays. Serum Tg reflected the presence or absence of cancer in 83% of 164 patients not receiving thyroxine (T4). This concordance improved to 97.5% in 158 patients tested while receiving T4. Thirty four patients in remission were tested both on and off T4 therapy; in all these patients the Tg level when receiving T4 was less than 5 ug/l. In 19 of 21 patients with cancer T4 treatment did not suppress Tg. Serum Tg thus provides an excellent marker for the presence or absence of thyroid cancer in patients taking T4, even if anti-Tg antibodies are present. It is proposed that monitoring of patients by assay of serum Tg should supplant routine assessment by radioactive-iodine scans of the neck or whole body. (Author abstract) (14 Refs)

22. URINARY GLYCOSAMINOGLYCAN EXCRETION AS A BIOCHEMICAL MARKER IN PATIENTS WITH BLADDER CARCINOMA.

Hennessey PT, Hurst RE, Hemstreet GP, Cutter G
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Cancer Res; 41(10):3868-3873 1981

Urinary glycosaminoglycan excretion was examined in 25 individuals with bladder cancer in comparison to glycosaminoglycan excretion by 8 normal individuals. Urinary glycosaminoglycan was isolated by gel filtration and quantified as macromolecular uronate concentration. Electrophoresis in calcium acetate and densitometry of Alcian blue-stained electrophoretograms were used to separate and quantify the relative amounts of individual glycosaminoglycans. Elevated excretion of macromolecular uronate was noted in 53% of the cancer cases. The highest levels were found among individuals with metastatic disease. Three electrophoretic bands were always detected in the control and cancer groups: chondroitin sulfate, heparin sulfate (both confirmed by chemical and enzymatic degradation), and a third band (Band 1) of unknown composition. A fourth band, corresponding to dermatan sulfate, was seen in some high-grade metastatic tumors. Band 1 excretion was elevated in a significant fraction of all patients. Seven of 12 metastastic cases but only 2 of 13 localized cases showed increased heparin sulfate excretion. Diagnostic limits were drawn from the observed distributions of normals, and with these limits 92% of the cancer cases, including 12 of 12 metastatic cases, could be identified. The results strongly suggest noninvasive urinary glycosaminoglycan analysis may well provide a new biochemical approach for detecting and monitoring the pathogenesis of bladder cancer. (Author abstract) (21 Refs)

23. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY QUANTITATION OF N-ACETYLNEURAMINIC ACID IN MALIGNANT MELANOMA AND BREAST CARCINOMA.

Silver HK, Karim KA, Gray MJ, Salinas FA
Cancer Control Agency British Columbia, 2656 Heather St., Vancer, B.C. V5Z 3J3, Canada
J Chromatogr; 224(3):381-388 1981

A rapid isocratic high-performance liquid chromatography (HPLC) method for quantitation of serum N-acetylneuraminic acid (NANA) is described. Separation is achieved on an Aminex HPX-87 cation-exchange resin using a 0.006 N sulfuric acid mobile phase. Compared with the more conventional thiobarbituric acid (TBA) method, HPLC is more reliable and has a much improved max sensitivity of 0.8 nmol/ml. In a limited study of malignant melanoma patients' sera, HPLC gave slightly higher values for NANA than TBA. In a more detailed study of breast carcinoma patients with measurable tumor burden, HPLC and TBA methods were used on the same sera and compared with concurrent carcinoembryonic antigen (CEA) determinations. HPLC resulted in a clear improvement in discrimination between tumor burden groups compared with either the TBA method or CEA. (Author abstract) (35 Refs)

24. ELEVATED URINARY LEVELS OF 6-HYDROXYMETHYLPTERIN DURING MALIGNANCY AND LIVER REGENERATION: A SIMPLE, NONINVASIVE TEST FOR CANCER DETECTION.

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Cancer; 48(7):1656-1663 1981

A simple and rapid method for determining urinary 6-hydroxymethylpterin levels is described. it involves adsorption of the pterin compound from deproteinized urine samples on activated charcoal under acidic conditions and its subsequent elution under alkaline conditions in a concentration suitable for its spectrophotofluorometric quantitation. The major blue fluorescent compound being measured was identified as 6-hyroxymethylpterin by thin layer chromatography on combined Silica gel-G and cellulose. While 30 healthy human subjects excreted 6-hydroxymethylpterin at a mean level of 0.121 ug/ml of urine, 120 patients with various types of cancer excreted very significantly higher levels ranging from 0.3 to 2.0 ug/ml. The mean excretion level for 19 patients with various nonmalignant diseases was 0.134 ug/ml which was not significantly different from that for the healthy control subjects. In two experimental model systems described, following partial hepatectomy and the induction of Yoshida ascites tumors in rats, the peak periods of liver regeneration and max tumor growth were accompanied, respectively, by 4-and 40-fold increases in urinary 6-hydroxymethylpterin excretion. Ingestion of multivitamin tablets containing 5 mg of folic acid (but not rich dietary sources of folates) resulted in temporary elevation of urinary 6-hydroxymethylpterin levels. The method described for determining urinary 6-hydroxymethylpterin provides a simple, noninvasive means of detecting prevailing malignancies. (Author abstract) (17 Refs)

25. TRANSFORMATION-ENHANCING ACTIVITY OF GELATIN-BINDING FRAGMENTS OF FIBRONECTIN.

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Proc Natl Acad Sci USA; 78(8):4965-4969 1981

Studies have established that cryoprecipitates of the plasma of tumor patients contain a biological activity enhancing morphological cell transformation (transformation-enhancing factor; TEF) in cultures of chicken embryo fibroblasts infected with temperature-sensitive mutants of Rous sarcoma virus. We report here that similar TEF activity is effected by defined fragments of human plasma fibronectin obtained by limited digestion with major humoral or tissue proteinases. TEF activity was obtained from plasminolytic fragments of fibronectin and from cathepsin G-treated fibronectin. No activity was recorded from intact dimeric fibronectin or its reduced and alkylated subunits, from fibrinogen or its plasminolytic fragments, or from plasmin (EC 3.4.21.7) or cathepsin G (EC 3.4.21.20) treated or untreated with proteinase inhibitors. All of the TEF activity of the proteolytic fragments of fibronectin was located on the gelatin-binding peptides. The minimum effective doses in the TEF assay were 750 ng/ml of plasmin-treated fibro nectin, 100 ng/ml of gelatin-binding plasminolytic fibronectin (enriched in Mr 180,000-190,000 polypeptides), and 100 ng/ml of gelatin-binding fragments of cathepsin G-treated fibronectin (enriched in a Mr 30,000 fragment). TEF activity of proteinase-treated fibronectin was inhibited by gelatin and by intact dimeric fibronectin. The potent TEF activity of proteolytic fragments of fibronectin raises the possibility that they may have a role in malignant transformation. (Author abstract) (32 Refs)

26. S-100 PROTEIN AS A NEW MARKER OF HISTIOCYTES (MEETING ABSTRACT).

Sato Y, Nakajima T, Watanabe S
Div. Pathology, Natl. Cancer Center, Chuo-ku, Tokyo 104, Japan
Nippon Monaikei Gakkai Kaishi; 21(1):104 1981

To determine the characteristics of the cells assumed to be histiocytes showing an S-100 protein-positive reaction, the presence or absence of S-100 protein in the histiocytes and monocytes in the bone marrow and blood of various tissues of the reticuloendothelial system was determined and compared immunocytochemically with other markers. In the superficial lymph nodes, cells containing S-100 protein were dispersed in the lymphatic sinus and paracortex area (T-zone region); these cells were stellate, having irregular projections. In the deep lymph nodes, there were generally few cells with S-100 protein. Tangible body macrophages at the active center had no protein S-100. The histiocytes containing S-100 protein generally had no lysozymes. In the spleen, only a few cells having S-100 protein were found in the white pulp. The granulocytes and monocytes in the bone marrow contained lysozymes but no S-100 protein. In the peripheral blood smear, lysozymes were found in granulocytes and monocytes, but there was no S-100 protein. From these findings, the S-100 protein-positive cells are assumed to have the same distribution as Langerhans cells and interdigitating reticulum cells. (no Refs) (In JPN)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

27. HODGKIN'S DISEASE: ESTABLISHMENT AND CHARACTERIZATION OF FOUR IN VITRO CELL LINES.

Diehl V, Kirchner HH, Schnadt M, Fonatsch C, Stein H, Gerdes J, Bole C
Dept. Hematology/Oncology, Inst. Genetics, Sch. Medicine, Karl-Wiechert-Allee 9, D-3000 Hannover, W. Germany
J Cancer Res Clin Oncol; 101(1):111-124 1981

Four in vitro cells established from the pleural effusions of two Hodgkin's disease (HD) patients and from the blood and bone marrow of a third were characterized morphologically, immunologically, and biochemically. The malignant nature of the cultured cells was confirmed by the presence of structural and numerical chromosome abnormalities, the monoclonality of marker chromosomes and the lack of Epstein-Barr virus-specific antigens. The cells gave rise to tumors in nude mice following intracranial transplantation and induced sc tumors when embedded on plasma dots before transplantation. All four lines were positive for Ia-like antigens, T-cell receptors, acid phosphatase, and acid esterase; they were negative for lysozyme peroxidase, chloracetate esterase, surface Ig or cytoplasmic Ig (CIg), and receptors for complement 3b, complement 3d, IgG-FC, and mouse or sheep RBC. Except for the lack of CIg in the in vitro cells, the marker pattern corresponded to that of Hodgkin's and Sternberg-Reed cells in biopsy material. The phenotype was not that of B cells, T cells, myeloid cells, monocytes, or macrophages. (26 Refs)

28. QUANTITATIVE IMMUNOFLUORESCENT ANALYSIS OF SURFACE PHENOTYPES OF MURINE B CELL LYMPHOMAS AND PLASMACYTOMAS WITH MONOCLONAL ANTIBODIES.

Lanier LL, Warner NL, Ledbetter JA, Herzenberg LA
Immunology Lab., Dept. Pathology and Medicine, Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131
J Immunol; 127(4):1691-1697 1981

In this study, a large series of murine B lymphomas and plasmacytomas were examined by quantitative flow cytometry analysis using a panel of monoclonal antibodies against murine differentiation antigens. These cell lines appear to represent subpopulations of lymphoid cells arrested at distinct stages of differentiation. In general, the pattern of reactions of these monoclonal antibodies with the B cell neoplasms was comparable to the reactions seen with normal cells in the same lineage. The Thy-1.2, Lyt-2, and T-30 differentiation antigens were not detected on any B lymphoma or plasmacytoma. However, certain surface Ig-positive B lymphomas do express the Lyt-1 antigen. With respect to other differentiation markers examined, including E2, F1, ThB, Lgp-100 (Ly 9.1), G2, and T-200 (Ly 5), the reaction of the B cell tumors reflected the expression of these markers on comparable normal cells. This investigation also emphasized the marked intratumor and intertumor heterogeneity that is observed when cloned cell lines are analyzed quantitatively for a large number of surface markers. Thus, this approach may be particularly useful in defining heterogeneity in maturation states within cloned tumor cell lines. (Author abstract) (33 Refs)

29. IMMUNOBIOLOGICAL PROPERTIES OF 1-BUTANOL-EXTRACTED CELL SURFACE ANTIGENS.

LeGrue SJ, Allison JP, Macek CM, Pellis NR, Kahan BD
Dept. Biochemistry, Surgery, Univ. Texas Health Science Center, Houston, Texas, 77030
Cancer Res; 41(10):3956-3960 1981

Extractions of viable 3-methylcholanthrene-induced murine sarcoma cells (MCA-F and MCA-2A) prepared using single-phase (2.5%) 1-butanol significantly retarded the outgrowth of the homotypic, but not the heterotypic, tumor of syngeneic C3H/HeJ mice. Butanol extracts specifically evoked a delayed hypersensitivity response in tumor-immune syngeneic mice, but not in alloimmune DBA/2J mice. Crude butanol ex tracts of MCA-F cells did not contain alloantigenic activity, as shown by their inability to block H-2 or Ia-specific antibodies in a complement-dependent cytotoxicity assay. Absorption of these same allospecific reagents with untreated or with butanol-extracted cells indicated that H-2 antigens remain associated with the cell surface during extraction. Thus, butanol appears to release tumor antigens, but not alloantigens, from the cell surface. (Author abstract) (31 Refs)

30. DISTRIBUTION AND MOLECULAR CHARACTERIZATION OF A CELL-SURFACE AND A CYTOPLASMIC ANTIGEN DETECTABLE IN HUMAN MELANOMA CELLS WITH MONOCLONAL ANTIBODIES.

Wilson BS, Imai K, Natali PG, Ferrone S
Dept. Molecular Immunology, Scripps Clinic Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037
Int J Cancer; 28(3):293-300 1981

The monoclonal antibodies 225.28S and 465.12 to human melanoma-associated antigens have been tested with a large va-

riety of surgically removed skin lesions and malignant tumors as well as with a panel of cultured cell lines in serological and immunochemical assays. The antibody 225.28S reacts with a plasma membrane antigen while the antibody 465.12 detects a cytoplasmic antigen. Both antibodies fail to react with melanocytes from normal skin as well as benign skin lesions but react with nevi, melanoma cells and some skin carcinomas. Analysis with surgically removed tumors and cultured human cell lines indicated that the plasma membrane antigen is restricted to skin lesions whereas the cytoplasmic antigen is synthesized by tumor cells of various histological origins. The plasma membrane antigen is composed of two glyco-polypeptides of 280,000 and greater than 440,000 daltons, while the cytoplasmic antigen consists of four glycopolypeptides of 94,000, 75,000, 70,000 and 25,000 daltons. None of these components are bridged by disulfide bonds. The cytoplasmic antigen was readily detected in the spent culture medium of melanoma cell lines in the form of a major 94,000 dalton and a minor 72,000 dalton structure, while the plasma membrane antigen was detectable only after vastly increasing the sensitivity of the assay system. (Author abstract) (23 Refs)

31. A HUMAN B-CELL LYMPHOMA SYNTHESIZING AND EXPRESSING SURFACE MU-CHAIN IN THE ABSENCE OF DETECTABLE LIGHT CHAIN.

Gordon J, Hamblin TJ, Smith JL, Stevenson FK, Stevenson GT
Lymphoma Res. Unit, Tenovus Res. Lab., Southampton General Hosp., Tremona Road, Southampton S09 4XY, England
Blood; 58(3):552-556 1981

Lymph node cells obtained from a case of non-Hodgkin's lymphoma, of follicular center cell histology, were seen by immunofluorescence to express Ig mu heavy chains but no detectable light chain on their surfaces. Antibody specific for determinants expressed only on uncombined mu-chain reacted with these cell surfaces, but not with normal or neoplastic cells expressing surface IgM. Analysis of radioiodinated surface material revealed mu-chains which, without reduction, migrated on SDS-gel electrophoresis as normal mu-chain monomers, and again failed to detect light chains. Lysates of cells incubated with 3H-leucine revealed the synthesis of mu-chains but not of light chains. The labeled mu-chains were not secreted into the culture supernatant, a finding confirmed in parallel cultures by radioimmunoassay. The findings are discussed with particular reference to current concepts of the 'mu-chain only' phenotype. (Author abstract) (35 Refs)

32. ON THE HETEROGENEITY OF MURINE NATURAL KILLER CELLS.

Minato N, Reid L, Bloom BR
Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, New York, NY, 10461
J Exp Med; 154(3):750-762 1981

The heterogeneity of natural killer (NK) cells in mice was analyzed. At least four phenotypically distinct cytotoxic effector cells that differ not only in their surface markers, but also in their responsivness to the regulatory influences of interferon (IFN) and interleukin 2 (IL-2) were identified. Cells from mouse spleen, bone marrow, and thymus of C57BL/6+/+(B/6), nu/nu, and be/be mice were cultured in medium for 4-5 days, and the cytotoxic activity of the nonadherent population was assayed against two different target cells, namely HeLa cells persistently infected with measles virus (HeLA-Ms), an NK-sensitive target similar to YAC-1, and P815 mastocytoma cells, an NK-resistant tumor cell. The effect of mouse IFN on the generation of three phenotypically distinct subsets of NK cells was determined. The results indicated that the subsets, NKI and NKM represent distinct and independent populations and that only the former is responsive to IFN. It was shown that the T cell growth factor preparation, IL-2, lacking IFN activity could stimulated NKT as well as T killer but not NKI or NKM cytotoxic activity. Experimental results also indicated that IFN and IL-2 act on phenotypically differents sets of cells. The results suggested that natural cytotoxicity in vitro can be mediated by several distinct cell populations under different genetic and regulatory control and indicated the importance of defining and delineating the cell lineages of each and the role of the independent subsets in resistance to virus infection. (25 Refs)

33. COMPLEMENT RECEPTORS ON LYMPHOCYTES.

Dierich MP
Hygiene-Institut der Universitat, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
J Cancer Res Clin Oncol; 101(1):65-67 1981

Complement (C)-coated sheep RBC (EA) were used to specify the C receptor activity of lymphocytes. RBC carrying C3b, C3bi, or C3d were used to specify the complement receptor activity of lymphocytes. Peripheral blood WBC interacted with all three cell types: EAC1-3b, 15% rosettes, EAC1-3bi, 18% rosettes, and EAC1-3d, 12% rosettes. After the elimination of monocytes and most T cells, peripheral blood WBC formed rosettes with 45%, 55% and 50%, respectively. Among Burkitt lymphoma-derived cell lines, Raji cells formed rosettes with 25%, 90% and 90%, respectively. Cells from the Daudi line did not interact with EAC1, but they reacted with C3bi-(70%) and C3d-(90%) cells. Human RBC reacted only with C3b-coated cells, whereas human monocytes and granulocytes were positive for both C3b- and C3bi- cells. The role of factor H (beta 1H) in the binding of C3bi is discussed. (10 Refs)

34. STAPHYLOCOCCAL PROTEIN A ENHANCES NATURAL KILLING ACTIVITY AGAINST LYMPHOID TUMOR CELL LINES.

Patel PC, Stefanescu-Soare I, Menezes J
(c/o Menezes) Lab. Immunovirology, Ste-Justine Hosp., 3175 Ste-Catherine Road, Montreal (Quebec) H3T 1C5, Canada
Int J Cancer; 28(3):277-284 1981

Protein A (pA), was found to augment the natural killing (NK) activity of peripheral blood lymphocytes against Burkitt's lymphoma-derived Raji and Daudi cells. This pA-enhanced NK activity was determined using the 51 Chromium release microcytotoxicity assay. It was found that the increased NK activity was dependent on the concentration of pA used. In addition, the pA-enhanced NK activity was dependent on the time of incubation of pA with the effector and target cell mixture. Pretreatment of effectors for 16 hr or more dramatically increased the NK activity against a wide range of tumor targets of different origin and possessing either B, T or null cell surface characteristics. The presence of the Epstein-Barr virus (EBV)-genome in the target cells did not influence the pA-enhanced NK activity. Nylon-wool column-fractionated, non-adherent lymphocytes (enriched in NK cells) showed an increased NK activity in the presence of pA than unfractionated lymphocytes. Pretreatment of certain targets with pA rendered them more sensitive to NK lysis. Interferon production was readily detected in supernatants from cultures of pA-treated effectors or effector-target mixtures, but not in supernatants from pA-treated target cultures tested. Results of different physicochemical treatments indicate that the pA-induced interferon

is of gamma type (Type II). Thus, the data presented suggest that the pA-induced enhancement of NK activity is most likely mediated by the pA-induced interferon. (Author abstract) (26 Refs)

35. SIALIC ACID METABOLISM IN REGENERATING RAT LIVER.

Kishore GS, Carubelli R
McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Lett; 13(4):281-289 1981

Sialic acid content and levels of the enzymes responsible for activation, transfer, and hydrolysis of sialic acids in the livers of control, sham-operated, and two-thirds-hepatectomized male rats were studied. At 24 and 48 hr after surgery, the specific activities of cytidine monophosphate-[4,5, 6,7,8,9-14C] N-acetylneuraminic acid (CMP-NANA) synthetase and sialyltransferase in regenerating liver, as well as in livers of sham-operated rats, were significantly higher than in control liver tissues removed at surgery. Combined range of values for the two enzymes (in nanomole/mg protein) were 401-452 vs 324 control and 0.47-0.57 vs 0.36 control, respectively. For each enzyme, values for regenerating and sham-operated liver were not significantly different. Membrane-bound neuraminidase activity was 2x control level in regenerating liver at 24 and 48 hr, but not significantly different from control in sham tissue. Cytosolic neuraminidase activity was similar in all tissue samples. Regenerating liver sialic acid content, determined by thiobarbituric acid assay, was lower at 24 but not at 48 hr than in sham or control liver samples; the changes were observed in whole liver homogenate and in the sedimentable fraction but not in the soluble fraction. Results for CMP-NANA synthetase and sialyltransferase did not constitute changes specifically associated with the regenerating process, since similar changes were seen in regenerating and sham-operated tissue. The selective increase in membrane-bound neuraminidase and decrease in sialic acid content in regenerating liver were of particular interest, in light of reduced activity observed for other regenerating rat liver acid hydrolases and increases in sialic acid seen in various malignant hepatic tissues. (27 Refs)

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. ANALYTICAL EVALUATION OF ABBOTT AND ROCHE CEA ASSAYS (MEETING ABSTRACT).

Stein KE, Valdes R
Division of Biochemistry, Department of Pathological Laboratory Medicine, Jewish Hospital, St. Louis, MO, 63110
Clin Chem; 27(6):1079 1981

We present data evaluating and comparing two carcinoembryonic antigen (CEA) radioimmunoassay methodologies; CEA-Roche and Abbott-CEA. Assay performance is characterized for reproducibility, recovery, CEA extraction efficiency, dilution parallelism, and method sensitivities. Roche CEA assays are performed utilizing the Amicon MC-40 diafiltration system. Analytical intra-run precision, determined for control material (Bio-Rad) and pooled human plasma, for the Roche Assay is 18% and 14.3% for concentrations of 1.8 and 9.6 ng/mL respectively. CEA added prior and subsequent to the recommended extraction procedures gives av recoveries of 85% and 94% respectively for the Abbott method. Plasma dilution over a wide range of concentration, 0.6 to 765 ng/mL, yields a linear correlation, observed (y) vs expected (x), y equals 0.96x + 0.3 ng/mL for Abbott and Y equals 1.04x + 5.4 ng/mL for Roche utilizing the indirect method and diluting dialysates for greater than 20 ng/mL. Corresponding regression analysis for values greater than 20 ng/mL utilizing the Roche direct assay was y equals 1.30x + 9.2 ng/mL indicating values at least 30% higher than expected by contrast to the indirect procedure or the Abbott method. The Abbott and Roche assay sensitivity coefficients for concentrations less than 5 ng/mL are 200 and 3,200 CPM per ng/mL respectively. In summary, comparable precision and dilution linearity are achieved by both assays as we perform them, provided the Roche assay utilizes the indirect method with dialysate dilution for values greater than 20 ng/mL, otherwise significant differences are observed. (no Refs)

2. ENDODERMAL SINUS TUMOUR AND ALPHAFOETOPROTEIN PRODUCTION BY OVARIAN TUMOURS (MEETING ABSTRACT).

Talerman A
Department of Pathology, University of Chicago, Chicago, IL
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

Endodermal sinus (Yolk sac) tumor (EST) became established as a distinctive type of germ cell neoplasm due to the exhaustive studies of Gunnar Teilum. He showed that homologous tumors showing the histological appearances of EST are found in the ovary, testis, and the extragonadal sites where germ cell tumors are known to occur. Although EST occurs in pure form, it is frequently associated with other neoplastic germ cell elements forming a mixed germ cell tumour. It has been shown that in the ovary EST is the second most common malignant germ cell neoplasm occurring from birth to the menopause. The recent finding that EST is associated with Alphafetoprotein (AFP) synthesis, which also occurs in the normal yolk sac during embryogenesis gave further support to the view that EST is a well differentiated but highly malignant germ cell neoplasm differentiating from embryonal carcinoma along the vitelline pathway. AFP has been shown to be a very good and specific tumor marker for EST, and it can be used for confirming the diagnos is, early detection of metastases and recurrences, and for monitoring the efficacy of therapy. (no Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

3. INTERPRETATION OF LDH ISOENZYME PATTERNS IN TESTICULAR CANCER (MEETING ABSTRACT).

Liu F, Fritsche HA, Trujillo JM
Department of Laboratory Medicine, University of Texas System Cancer Center, Houston, TX
Clin Chem; 27(6):1066 1981

We have observed abnormal levels of serum lactic dehydrogenase-1 (LDH-1) activity in 81% (34/42) of patients with advanced stage III germ cell malignancy of the testis. Our criteria for evaluating the electrophoretic isoenzyme pattern were as follows: Criterion 1, LDH-1 value in absolute units greater than 52.0 IU/L with the LDH-1/Total ratio greater than 37.2%; Criterion 2, the absolute value of LDH-1 less than 52.0 IU/L but the LDH-1/Total LDH ratio greater than 37.2%; Criterion 3, the absolute value of LDH-1 greater than 52 IU/L and its relative ratio lower than 37.2% activity but the LDH-5/LDH-1 ratio less than 0.5, or when the LDH-5/LDH-1 ratio is greater than 0.5 but the LDH-1 greater than LDH-2. Interpretation of LDH-1 activity only on the basis of its relative ratio regardless of total LDH value (criterion 1 and 2) identified a total of 28 patients (67%). A criterion 3 elevation was demonstrated in 6 (14%) additional patients. LDH-1 elevation occurred in all histopathologic cell types. The frequency of LDH-1 elevation correlated with the extent of the disease (stage III-B-1 and 2, 50%; stage III-8-3, 85%; stage III-B-4, 91%; stage III-B-5, 93%). All patients with persistent elevations or re-elevations of LDH-1 have shown progressive or recurrent disease and patients with no clinical evidence of disease have demonstrated normal LDH-1 values. In those patients with elevated LDH-1 activity, serial measurements of serum LDH-isoenzyme reflect the response of the patient to therapy. (no Refs)

4. THE PROGNOSTIC VALUE OF PRESENTING SERUM LDH IN NON-HODGKIN LYMPHOMA.

Ridgway D, Smiley S, Neerhout RC
Dept. Pediatrics, Univ. Oregon Health Sciences Center, 3181 S. W. Sam Jackson Park Road, Portland, OR, 97201
J Pediatr; 99(4):611-613 1981

Serum lactate dehydrogenase (LDH) and disease course were reviewed in 23 consecutive pediatric patients (26 mo-17 yr old) with non-Hodgkin's lymphoma (10 Burkitt, 3 diffuse histiocytic, 8 diffuse lymphoblastic, and 2 undifferentiated non-Burkitt lymphomas) seen over a 48-mo period. Of the 23 patients, 22 were treated with multi-drug chemotherapy. The serum LDH value at diagnosis ranged from 160-6,100 IU/liter (IU/L). Of the 23 patients, 9 had presenting LDH values greater than 500 IU/L and 8 of these patients relapsed or died; one child whose initial LDH was 600 IU/L remained alive and was in continuous remission 22 mo after diagnosis. Among 14 patients with presenting LDH values less than 500 IU/L, a single relapse occurred in one child 24 mo after diagnosis. He remained alive and in remission on therapy 44 mo after diagnosis. The other 13 children were in continuous first remission from 3-45 mo after diagnosis. In the total patient group, a strong as-

sociation between presenting LDH values greater than 500 IU/L and eventual relapse and death (P less than 0.01) was observed. Results indicated that serum LDH is a reliable indicator of current disease status for patients with non-Hodgkin lymphoma and a useful confirmation of remission status; it cannot be used to predict impending return of disease. (10 Refs)

5. CLINICAL UTILITY OF LEUKEMIA CELL TERMINAL TRANSFERASE MEASUREMENTS.

McCaffrey R, Lillquist A, Sallan S, Cohen E, Osband M

Section Medical Oncology, Evans Dept. Clinical Res., Univ. Hosp., Boston, MA

Cancer Res; 41(11,part2):4814-4820 1981

Interest in the DNA-synthetic enzyme terminal deoxynucleotidyl transferase (TdT) has developed from two sets of observations: first, in normal animals, it occurs only in immature thymic lymphocytes and in a subpopulation of bone marrow lymphocytes: second, it is present in the blast cells of almost of all patients with acute lymphoblastic leukemia. A prospective trial to evaluate blast cell TdT as a predictor of responsiveness to vincristine and prednisone in 30 Philadelphia chromosome-positive patients with blastic chronic myelogenous leukemia was undertaken. Eleven of 16 TdT-positive patients responded, whereas only 1 of 14 TdT-negative patients showed improvement. Among TdT-positive patients under the age of 50 yr, the response rate was 78%. Enzyme-negative patients under the age of 50 had an 11% response rate. Blast cell morphology (ie, lymphoblastic vs myeloblastic) had no significant correlation with either responsiveness or TdT activity. These results suggest that blast cell TdT activity may identify leukemic patients who are likely to respond to vincristine and prednisone irrespective of their conventional classification. (Author abstract) (49 Refs)

6. COMPARATIVE STUDY OF GAMMA GLUTAMYL TRANSFERASE, ALKALINE PHOSPHATASE AND ITS ALPHA1 ISOENZYME AS BIOLOGICAL INDICATORS OF LIVER METASTASES.

Viot M, Thyss A, Viot G, Ramaioli A, Cambon P, Schneider M, Lalanne CM

Centre Antoine-Lacassagne, 36 Voie Romaine, 0654 Nice Cedex, France

Clin Chim Acta; 115(3):349-358 1981

Serum of patients with various malignant diseases (331) and of healthy controls (101; 48 male, 53 female) was compared. The alpha1 isoenzyme of alkaline phosphatase (AP) was determined relative to the variation of total AP (TAP) and gamma glutamyl transferase (GGT) levels. TAP and GGT were assayed on the Centrifichem System 400. Electrophoretic fractionation of samples allowed identification of four AP isoenzymes: alpha1 AP (a1AP), liver, bone and intestine fractions. Studies were conducted in patient groups without secondary hepatic lesions (101) and those with liver metastases (75); and in groups with alcoholic cirrhosis (24) and with acute viral hepatitis (30). Compared to GGT and TAP, the a1AP test was more sensitive and more specific being capable of detecting 97% of the liver metastases with a specificity of 90%. (27 Refs)

7. INCREASED INACTIVE CREATINE KINASE B PROTEIN IN THE PLASMA OF PATIENTS WITH MALIGNANCY.

Burnam MH, Barstis JL, Stern CS, Rose DM, Crouch MA, Haskell CM, Singh BN

Cardiology Section (691/111E), Wadsworth Veterans Admin. Medical Center, Wilshire and Sawtelle Blvd., Los Angeles, CA, 90073

Clin Chem; 27(10):1724-1728 1981

Using a specific radioimmunoassay for enzymically inactive creatine kinase (EC 2.7.3.2) B protein (CK-Bi), we studied 139 patients with various malignancies. We found it to be increased in certain adenocarcinomas, including colorectal, lung, and prostate, as has also been reported for enzymically active CK-BB. Of 15 patients with leukemia or lymphomas with active disease, 12 also had increased values for CK-Bi in plasma. In these patients, concentrations of CK-Bi in plasma tended to correlate with disease activity, increasing with aggressive malignancy and decreasing on successful treatment. Thus, measurement of CK-Bi may constitute a sensitive means for detecting malignancy and, in certain subsets of patients, for monitoring therapeutic response. (Author abstract) (15 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

8. DISTRIBUTION OF CYTOPLASMIC AND NUCLEAR ESTROGEN RECEPTORS IN HUMAN BREAST CANCER (MEETING ABSTRACT).

Genz T, Eiletz J

Universitats-Frauenklinik Charlottenburg, Berlin, W. Germany

Acta Endocrinol [Suppl]; 96(240):123 1981

In our study estrogen receptor levels were measured in both compartments of breast cancer tissues. Cytoplasmic estrogen and progesterone receptors were determined by the dextran-coated charcoal technique. Measurement of nuclear binding sites was performed by an exchange assay with some modifications according to Bayard et al. For any sample to be classed as positive in terms of estrogen receptors it had to satisfy the following criteria: yield an unambiguous Scatchard line, levels of 20 fmol/mg protein and 25 fmol/mg DNA for cytoplasmic and nuclear binding sites, respectively. Nuclear receptor values ranged from 25-3,000 fmol/mg DNA with a dissociation constant of approx 3 x 10(-9) M to 12 x 10(-10) M. Eighty tissues (59%) with positive cytoplasmic estrogen receptor contained significant levels of nuclear binding sites in 84.3% of the specimens with and in 73.9% of the specimens without additional cytoplasmic progesterone receptors. Estrogen receptor negative tumors had low levels of nuclear binding sites in 17% only. Different results in receptor distribution in both fractions were found in approx 20% of all breast cancer cells. Preliminary clinical results indicate that the additional measurement of nuclear binding sites for estradiol may give more detailed information about hormone dependence. Fourteen women with metastatic disease could be analyzed. Nine of them had an objective remission undergoing hormone therapy. There was a good correlation between positive as well as negative cytoplasmic and nuclear binding sites in responders and non-responders, respectively. (no Refs)

9. INCIDENCE OF HCG SUBUNITS IN PATIENTS WITH HCG-POSITIVE NONSEMINOMATOUS TESTICULAR GERM CELL TUMORS (MEETING ABSTRACT).

Mann K, Haidl P, Hammerl B, Karl HJ
Universitat Munchen, Munich, W. Germany
Acta Endocrinol [Suppl]; 96(240):80 1981

Human chorionic gonadotropin (HCG) determinations in serum are widely accepted to be useful as tumor markers in testicular cancer. Most anti-hCG-beta antisera available are sufficiently specific with respect to their cross-reactivity with pituitary hormones, but the interference of hCG subunits in heterologous hCG-beta radioimmunoassays is poorly explored. In order to evaluate the incidence of hCG subunits in sera with elevated hCG levels hCG, hCG-beta, and hCG-alpha were determined simultaneously using specific assays, 125I-hCG, anti-hCG-beta Serono, 125I-hCG-beta, anti-hCG-beta Union Carbide and 125I-hCG-alpha, anti-hCG-alpha 'Irmi'. Data of subunit determinations were corrected respecting the 2.2% cross-reactivity of hCG in the homologous hCG-beta assay and 6.4% in the alpha-assay. HCG and hCG-alpha levels were compared in 40 patients with nonseminomatous germ cells tumors. hCG, hCG-beta, and hCG-alpha in 25. The control group consisted of male patients without neoplastic, chronic inflammatory, thyroid or renal diseases. Labeled hCG, hCG-beta and hCG-alpha donated from NIAMD, was cochromatographed as an internal standard. Blue dextran, 125I and labeled hormones were also gel filtered in separate experiments for calibration. Five (20%) out of 25 hCG positive patients showed elevated hCG-beta levels and of 40 patients 4 (10%) had elevated hCG-alpha levels. Definite proof of subunit secretion was performed in 3 cases by gel chromatography of the patients' sera. In one patient immunoreactive hCG-beta showed two peaks, corresponding to 125I-hCG-beta and a high molecular from. HCG-alpha eluted in an identical position with 125I-hCG-alpha. These data demonstrate that hCG subunit secretion in patients with elevated hCG levels is not a negligible rare event and support our proposal that, for routine purposes, a hCG assay is preferable, which makes it possible to determine hCG and hCG-beta simultaneously on parallel standard curves, standardized with the 2nd Internatio nal Reference Preparation of hCG. (no Refs)

10. CHARACTERIZATION OF A SMALL MOLECULAR SIZE URINARY IMMUNOREACTIVE HUMAN CHORIONIC GONADOTROPIN (HCG)-LIKE SUBSTANCE PRODUCED BY NORMAL PLACENTA AND BY HCG-SECRETING NEOPLASMS.

Masure HR, Jaffee WL, Sickel MA, Birken S, Canfield RE, Vaitukaitis JL
(c/o Vaitukaitis) Section Endocrinology and Metabolism, Boston City Hosp., 818 Harrison Ave., Boston, MA, 02118
J Clin Endocrinol Metab; 53(5):1014-1020 1981

Urine obtained from normal pregnant women as well as from patients with hCG-secreting tumors frequently contains native hCG and free hCG subunits when separated on Sephadex G-100. In addition, a small amount of an immunoreactive, hCG-like, low mol wt substance is usually observed in those chromatograms and represents less than 1% of the total immunoreactive hCG present. Two patients with widely metastatic hCG-secreting tumors excreted disproportionately large quantities of that low mol wt substance, and that observation raised the possibility that this substance was a secretory and not a degradative product of the hCG molecule. The small immunoreactive hCG-like substance was subsequently characterized immunologically, biologically, and physically. The hCG fragment displayed a biphasic dose-response line in a homologous hCG RIA. The slope of the upper portion of the dose-response line was equal to that for native hCG, but the slope of the lower component of the dose-response line was significantly different from that for hCG. The immunoreactive hCG substance cross-reacted with hCGbeta but not with either hCGalpha or hCGbeta carboxyl-terminus. The small molecular size immunoreactive hCG-like substance bound to Concanavalin A-Sepharose 4B and eluted with 0.2 M alpha-D-methyl glucopyranoside, contained no significant intrinsic biological activity when tested in the in vitro Leydig cell bioassay and also failed to compete with labeled hCG for specific ovarian LH/hCG receptors. Consequently, that small urinary immunoreactive hCG substance behaved neither as a hCG agonist or antagonist. It exhibited a plasma half-life of 4.5 min when the appropriate Sephadex G-100 fractions were injected into immature female rats. The small molecular size immunoreactive hCG-like substance may be a secretory or breakdown product of hCG-secreting cells. (Author abstract) (26 Refs)

11. PROSTACYCLINS IN PROSTATIC CANCER: A POTENTIAL NON-SPECIFIC TUMOUR MARKER (MEETING ABSTRACT).

Khan O, Hensby CN, Williams G
No affiliation given
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Prostaglandins have been implicated in many disease states, including the development and spread of malignant tumors. Gas chromatography and mass spectrometry (GC-MC) of prostanoids and thei r metabolites in various human biological specimens (plasma, urine and benign and malignant tissues) have been analyzed by us. The stable derivative of prostacyclin, (PGI2) is 6-oxo-PGF1alpha was selectively studied. This prostanoid is known to be a potent hormone in inducing bone resorption. In age matched, healthy volunteers, the mean circulating level of 6-oxo-PGF1alpha was 98.5 +/-4.2 picograms/ml, while in patients with a benign prostatic enlargement it was 107.36 +/-8.25 picograms/ml. Whereas, untreated patients with prostatic cancer had a significant increase of 224 +/-3.62 picograms/ml and that in patients with skeletal metastases was even higher. The plasma concentration of 6-oxo-PGF1alpha varied with tumor differentiation and was higher in those patients with a poorly differentiated tumor. These estimations were prior to a rectal examination of the prostate gland. The plasma levels of patients with other tumors (breast, lung, colon, uterus and bladder) prior to treatment were also analyzed and found to be significantly elevated. Painful metastases were associated with raised prostaglandin levels and the biochemical effect of a prostaglandin synthetase inhibitor (Flubiprofen) will be described in over 60 patients. Standard hormonal therapy caused a significant fall in 6-oxo-PGF1alpha levels. Persistently elevated levels were associated with a worsening prognosis. Rising levels correlated with disease progression (by bone scan) and were a more accurate indicator than serum acid phosphatase. (no Refs)

12. THE DIAGNOSTIC DILEMMA OF THE 'SMALL ROUND CELL NEOPLASM': CATECHOLAMINE FLUORESCENCE AND TISSUE CULTURE MORPHOLOGY AS MARKERS FOR NEUROBLASTOMA.

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Cancer; 48(9):2088-2094 1981

Small round cell neoplasms, which include neuroblastoma, Ewing's sarcoma, embryonal rhabdomyosarcoma, oat cell carcinoma, and lymphoma, are often confused with one another histologically. The advent of successful but distinct therapeutic approaches for different neoplasms has increased the need for precise diagnosis. The use of techniques ancillary to routine histologic or ultrastructural analysis allows better definition of the specific tumor type. Four cases of small cell tumor are described in which the initial working diagnosis was incorrect. The application of two diagnostic procedures for neuroblastoma was of great value in clarifying the proper diagnosis. These tests were a rapid fluorescence assay for intracellular catecholamines and a tissue culture assay for neurite outgrowth. Both of these methods are highly sensitive for neuroblastoma and distinguish neuroblastoma from other small round cell neoplasms. Their use confirmed this unsuspected diagnosis in three cases and excluded neuroblastoma in the fourth case. (Author abstract) (39 Refs)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

13. HUMAN LEUCOCYTE ANTIGENS.

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Haematol Blood Transfus; 26:309-313 1981

Bone marrow progenitor cells were characterized and stages of T lymphocyte differentiation traced using monoclonal antisera. Bone marrow cells were treated with antimyeloid antibody, which lysed about 50% of the cells, primarily myelocytes and metamyelocytes. After staining with anti-HLe-1 the remaining cells were sorted. Weakly staining cells accounting for less than 2% of total marrow nucleated cells were collected. This fraction contained myeloid and erythroid progenitors and cells with the nuclear enzyme TdT. The TdT-bearing cells were probably lymphoid progenitors and had the phenotype HLe+-TG-1-. About 5% of intrathymic cells were large and lacked the cortical thymic marker HTA-1. The earliest cortical cells lacked HLA-A, -B, and -C antigens, which the presumed marrow progenitor cells possessed. Some early cortical cells possessed TdT and OKT9 markers. Medullary cells resembled peripheral T cells in lacking HTA-1 and TdT but regaining HLA. Thymic phenotypes showed heterogeneity paralleling that shown by leukemic cells, indicating that caution should be used in identifying phenotypes as abnormal. Analysis of peripheral lymphoid cells suggested that UCHT1 antigen is a marker for mature T cells. (17 Refs)

14. EXPRESSION OF MYELOID DIFFERENTIATION ANTIGENS ON NORMAL AND MALIGNANT MYELOID CELLS.

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J Clin Invest; 68(4):932-941 1981

A series of monoclonal antibodies have been characterized that define four surface antigens (MY3, MY4, MY7, and MY8) of human myeloid cells. They were derived from a fusion of the NS-1 plasmacytoma cell line with splenocytes from a mouse immunized with human acute myelomonocytic leukemia cells. MY3 and MY4 are expressed by normal monocytes and by greater than 90% of patients with acute monocytic leukemia or acute myelomonocytic leukemia, but are detected much less often on other types of myeloid leukemia. MY7 is expressed by granulocytes, monocytes, and 5% of normal bone marrow cells. Seventy nine percent of all acute myeloblastic leukemia (AML) patients tested (72 patients) express MY7 without preferential expression by any AML subtype. MY8 is expressed by normal monocytes, granulocytes, all peroxidase-positive bone marrow cells, and 50% of AML patients. MY3, MY4, and MY8 define myeloid differentiation antigens in that they are not detected on myeloid precursor cells and appear at discrete stages of differentiation. These antigens are not expressed by lymphocytes, RBC, platelets, or lymphoid malignancies. The monoclonal antisera defining these antigens have been used to study differentiation of normal myeloid cells and malignant myeloid cell lines. (Author abstract) (49 Refs)

15. CLASSIFICATION OF HUMAN LEUKEMIA BY MEMBRANE ANTIGEN ANALYSIS WITH XENOANTISERA.

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Cancer Res; 41(11,part2):4781-4785 1981

Rabbit and monkey antisera after appropriate absorption were rendered specific for normal or leukemic lymphoid- and myeloid-associated antigens. Antisera defining a common peripheral blood T-cell antigen, a thymus leukemia antigen, HLA-DR or Ia-like antigen (CALLA) common acute lymphoblastic leukemia antigen, and a myeloid-monocyte (M) antigen were used in a microcytotoxicity assay to classify leukemic cells from 30 patients in a double blind study. The antisera to the M antigen reacted with adherent peripheral blood cells and polymorphonuclear leukocytes and failed to react with nonadherent mononuclear cells and enriched T-cells and chronic lymphocytic leukemia cells. The M antisera also reacted with U937, a monocytic-type cell line, and with HL60, a promyelocytic-type cell line, but failed to react with T and B lymphoblastoid cell lines. The specificities of the other antisera have been described in previous reports. Cells from three of the patients could not be phenotyped by microcytotoxicity testing. Cells from 25 patients had a consensus morphological or histochemical diagnosis of either acute lymphoblastic leukemia or acute nonlymphocytic leukemia. The serological classification of these patients using the five types of antisera listed above were consistent with the consensus diagnosis. In addition, the lymphoid cancers were further sub-classified as to T-, B-, or thymus antigen types. There was no consensus lymphoid versus myeloid diagnosis on cells from two patients. The serological classification in both cases favored a diagnosis of myeloid rather than lymphoid leukemia. (Author abstract) (20 Refs)

16. USE OF MONOCLONAL ANTIBODIES AS DIAGNOSTIC AND THERAPEUTIC REAGENTS IN ACUTE LYMPHOBLASTIC LEUKEMIA.

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Cancer Res; 41(11,part2):4771-4775 1981

A monoclonal antibody specific for a common acute lymphoblastic leukemia (ALL) antigen has been generated and characterized. This antibody (J-5) is reactive with leukemic cells from most patients with non-T-cell ALL and some patients with chronic myelocytic leukemia in blast crisis. J-5 antibody is not reactive with leukemic cells from patients with either T-cell ALL, chronic lymphocytic leukemia, acute myeloblastic leukemia, or stable-phase chronic myelocytic leukemia. In addition to diagnostic applications, anti-common ALL antigen monoclonal antibody has been used to study the effect of specific serotherapy in the treatment of ALL. In the first patient with ALL treated with J-5 antibody, a 90% reduction in circulating lymphoblasts occurred within 1 hr of starting antibody infusion. Despite continued serotherapy, however, lymphoblasts persisted in peripheral blood and bone marrow. Analysis of cell surface markers during serotherapy suggested that resistance to antibody-mediated lysis in vivo may have been due to antigenic modulation of leukemic cells in response to J-5 monoclonal antibody. (Author abstract) (27 Refs)

17. USE OF MONOCLONAL ANTIBODIES, MORPHOLOGY, AND CYTOCHEMISTRY TO PROBE THE CELLULAR HETEROGENEITY OF ACUTE LEUKEMIA AND LYMPHOMA.

LeBien TW, McKenna RW, Abramson CS, Gajl-Peczalska KJ, Nesbit ME, Coccia PF, Bloomfield CD, Brunning RD, Kersey JH
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Cancer Res; 41(11,part2):4776-4780 1981

A combined immunological, morphological, and cytochemical approach to the study of malignant cells in patients with acute leukemia and lymphoma is presented. Newly produced monoclonal antibodies that bind to antigens of human mononuclear cells (TA-1), or B-lymphocytes (BA-1) were used to study malignant cells from patients with acute lymphoblastic leukemia (ALL), acute myelocytic leukemia, acute myelomonocytic leukemia, and chronic lymphocytic leukemia. Results in lymphoid leukemia-lymphoma patients were compared with other immunological markers and indicate that the major groups of ALL and childhood non-Hodgkin's lymphoma are T-ALL, pre T-ALL, pre-B-ALL, and non-T, non-B-ALL. In addition, each major group had multiple phenotypes when analyzed with seven immunological markers including the RBC rosette receptor, surface Ig, cytoplasmic Ig M, the early lymphocyte-acute lymphoblastic leukemia antigen, monoclonal antibody TA-1, monoclonal antibody BA-1, and a monoclonal antibody against HLA-Dr. While immunological heterogeneity was demonstrable within each group, distinct biological behavior was observed, with T-ALL and B-ALL generally presenting as 'lymphomas' and the others presenting as 'leukemias.' Morphological analysis using the French-American-British classification provided independent information in the definition of groups with differing clinical behavior. Cytochemical analyses demonstrated focal paranuclear staining of leukemia cells with acid phosphatase in 73% of T-ALLs and 6% of non-T, non-B-ALLs. (Author abstract) (32 Refs)

18. MONOCLONAL ANTIBODY AGAINST A BURKITT LYMPHOMA-ASSOCIATED ANTIGEN.

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Proc Natl Acad Sci USA; 78(10):6485-6488 1981

A monoclonal antibody, referred to as 38.13, was obtained by fusing murine myeloma cells with Lewis rat splenocytes sensitized with Daudi cells (human Burkitt lymphoma containing Epstein-Barr virus genome but lacking HLA-A, -B, and -C and beta2-microglobulin molecules at the cell surface). 38.13 antibody was demonstrated to be a rat IgM. By complement-dependent microcytotoxicity and indirect immunofluorescence assays, 38.13 antibody was shown to react specifically with cells derived from Burkitt tumors, including both Epstein-Barr virus genome-carrying and Epstein-Barr virus-negative Burkitt lymphoma. By contrast, Epstein-Barr virus-containing lymphoblastoid cell lines derived from normal B lymphocytes were not recognized by 38.13 antibody. Fresh malignant cells from patients affected with various lymphoproliferative disorders were negative, except 4/8 having abdominal Burkitt-like lymphomas. Normal lymphocytes from peripheral blood, spleen, lymph node, tonsil, and bone marrow and mitogen (phytohemagglutinin, pokeweed mitogen, and concanavalin A)-activated blasts were also negative. Thus, 38.13 antibody apparently recognized a Burkitt-associated antigen that is not related to Epstein-Barr virus. The pattern of reactivity of 38.13 antibody with various Burkitt lymphoma cells appeared quite heterogenous and some Burkitt cells were consistently negative. 38.13 antibody thus defines a subset of Burkitt lymphomas. (Author abstract) (18 Refs)

19. DETECTION OF MAMMARY-CARCINOMA CELLS IN MARROW USING ANTISERA TO EPITHELIAL-MEMBRANE ANTIGEN (MEETING ABSTRACT).

Dearnaley DP, Sloane JP, Ormerod MG, Steele K, Coombes RC, Neville AM
Institute for Cancer Research, Sutton, Surrey, England
Br J Cancer; 43(5):727 1981

We have previously described an epithelial membrane antigen (EMA) which can be demonstrated by immunohistochemical methods on formalin-fixed, paraffin-embedded sections of human tissue. EMA is confined to but widely distributed in epithelial tissues and tumors derived from them and has been used to detect micrometastases in histological section. We have developed a technique using an alkaline phosphatase conjugate for staining smears of marrow. Giemsa, Luke's and anti-EMA preparations were made from 74 posterior-iliac-crest marrow aspirates from patients with breast cancer. Anti-EMA staining revealed malignant cells in 15 patients, compared with 7 demonstrated by conventional methods. The 5 patients with greater than 100 EMA-positive cells/smear were all diagnosed as malignant on Giemsa or Luke's preparations, but only 2/12 with less than 100 positive cells/smear were detected. Ten/24 patients with bone metastases had EMA-positive smears, as did 4/20 patients with disseminated disease but without bone involvement. Twenty patients had apparently localized primary breast cancer, one of who had EMA-positive cells in the marrow, as did one/10 patients thought to be free of metastases during follow-up. Less than 5 EMA-positve cells were found in the specimens from these patients. This technique may be capable of detecting micrometastatic disease in breast cancer, as well as improving the detection of marrow involvement in patients with disseminated disease. Further studies are being undertaken to determine wheth-

er larger quantities of marrow from multiple sites will enable the detection of micrometastatic disease in patients with poor-risk primary breast cancer. (1 Ref)

20. PROLYMPHOCYTIC LEUKEMIA.

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Ugeskr Laeger; 143(37):2339-2343 1981

Recent studies on prolymphocytic leukemia (PLL) are reviewed. In a series of 53 patients, there were 32 men and 21 women (40-87 yr old, median age 67 yr). Splenomegaly was found in 53/53 cases, hepatomegaly in 25/53, lymph node involvement in 10/53, skin infiltration in 8/53, lymphocytosis in 53/53, anemia in 50/50, and thrombocytopenia in 31/50. The immunological characteristics were investigated in 34 patients: B-cell markers were found 23/34 cases, T-cell markers in 10/34, and both B- and T-cell markers in 1/34. Dominance of prolymphocytes with typical nuclear structure in the blood and bone marrow is characteristic of PLL. The cases derived from B lymphocytes appear to be related immunologically to non-Hodgkin's lymphoma, and the B prolymphocyte can be differentiated immunologically from the lymphocyte of B-cell chronic lymphocytic leukemia. The survival of the patients is short, ranging from wk to mo, and the patients do not respond to the current therapy for chronic lymphocytic leukemia. The best therapeutic results to date are achieved by splenectomy combined with leukapheresis or polychemotherapy as employed in non-Hodgkin's lymphoma. (28 Refs) (In DAN)

21. A CLINICAL PERSPECTIVE ON CELL MARKERS IN ACUTE LYMPHOCYTIC LEUKEMIA.

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Cancer Res; 41(11,part2):4794-4801 1981

Two hundred consecutive new patients, with acute lymphocytic leukemia (ALL) have been studied with a battery of five cell marker assays to determine if a classification system with prognostic significance can be developed; 182 have been classified among four groups as follows: 33 T-cell, 3 B-cell, 126 common, and 20 undifferentiated ALLs. Patients with T-cell disease are likely to have unfavorable clinical prognostic features and a poor response to therapy. Rare patients with B-cell disease are closely related clinically to non-Hodgkin's lymphoma. Those with common ALL infrequently have unfavorable clin ical features and have a superior outcome to that of T-cell patients. Children with undifferentiated markers seem to respond less well to treatment than do those with common ALL, yet may not be identifiable as poor risk by clinical features. What remains to be resolved with further observation is whether these marker patterns are more reliable indicators of prognosis than the usual clinical determinants predisposing to treatment failure (high WBC count, mediastinal mass, and CNS disease). At the present time, it appears that in the absence of poor-risk clinical prognostic features, patients with common ALL are more likely to have lasting remissions than those with RBC-rosette-positive T-cell disease or those with ALL that is undifferentiated by markers. (Author abstract) (9 Refs)

22. RELEVANCE OF SURFACE MARKERS IN CHRONIC LYMPHOCYTIC LEUKEMIA TO ACUTE LYMPHOCYTIC LEUKEMIA.

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Cancer Res; 41(11,part2):4810-4813 1981

The surface membrane of the B-lymphocyte of chronic lymphocytic leukemia (CLL) has been subject to detailed investigation over the past decade. Surface Ig of low density, punctate in distribution, without the tendency to polar cap formation, and clonal with respect to light and heavy chains, is characteristic. Other B-cell properties include the presence of the Ia antigen and the receptor for the C3d portion of complement. The CLL surface membrane lacks such T-cell attributes as the ability to form rosettes with sheep RBC and reactivity with anti-T-cell antisera, although T-cells may be increased early in the disorder. CLL is believed to be a proliferation of a B-lymphocyte of the medullary cord of the lymph node, although the exact place of this cell in lymphocyte development remains to be clarified. Surface markers are useful in distinguishing classical B-cell CLL from other proliferations of small lymphocytes (lymphosarcoma cell leukemia of follicle-center B-cells, T-cell CLL, Sezary syndrome, and reactive lymphocytosis). (Author abstract) (36 Refs)

23. PREDICTIVE ABILITY OF LUKES-COLLINS CLASSIFICATION FOR IMMUNOLOGIC PHENOTYPES OF CHILDHOOD NON-HODGKIN LYMPHOMA: AN INSTITUTIONAL SERIES AND LITERATURE REVIEW.

Crist WM, Kelly DR, Ragab AH, Roper M, Dearth JC, Castleberry RP, Flint A
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Cancer; 48(9):2070-2075 1981

Tissues from 22 children with non-Hodgkin lymphoma (NHL) were studied pathologically and immunologically. Most children were noted to have marked (B- or T-cell) neoplasms and the Lukes-Collins classification was predictive of immunologic phenotype in cases where markers were presented. Our series and a review of the literature demonstrates that most abdominal NHL are B-cell in origin and are oft en small noncleaved follicular center cell lymphoma (Burkitt type). Most mediastinal primary lesions are T-cell in origin and of convoluted cell morphology. a few neoplasms (often peripheral nodal) lack the characteristic surface Ig or RBC rosetting properties of B- or T-cell lesions, respectively. Frequently marrow and CNS involvement are observed in T-cell lymphomas and are not infrequent in B cell neoplasms. Shared immunologic and clinical features between the B- or T-cell lymphomas and their leukemic counterparts support the concept that they often differ only in the stage of disease progression. (Author abstract) (22 Refs)

24. SOUTHWEST ONCOLOGY GROUP EXPERIENCE WITH IMMUNOLOGICAL PHENOTYPING IN ACUTE LYMPHOCYTIC LEUKEMIA OF CHILDHOOD.

Pullen DJ, Falletta JM, Crist WM, Vogler LB, Dowell B, Humphrey GB, Blackstock R, Van Eys J, Cooper MD, Metzgar RS, Meydrech EF
Operations Office, Southwest Oncology Group, 3500 Rainbow Blvd., Suite 100, Kansas city, KS, 66103
Cancer Res; 41(11,part2):4802-4809 1981

The Pediatric Division of the Southwest Oncology Group is attempting to define subgroups of acute lymphoblastic leukemia (ALL) by laboratory delineation of marrow lymphoblast characteristics at diagnosis. Immunological subclassification studies include erythrocyte-forming rosette (E-rosette), C3 receptor, Fc receptor, surface Ig (Sig) and cytoplasmic Ig (CIg) determinations, as well as peripheral T (PT), thymocyte, Ia, and common ALL membrane antigen testing. Four subgroups of ALL have thus far been defined: null (SIg-, CIg,-, PT-); pre-B (SIg-, CIg+, PT-); B-cell (SIg+, CIg-, PT-); and T-cell (SIg-, CIg-, PT+). A group of 118 patients have had complete testing, and an additional 121 patients have had partial testing. Thirty-five patients with pre-B ALL and 27 patients with T-cell ALL have thus far been studied. Pre-B and null types of ALL appear closely related in multiple subclassification parameters (age, sex, physical findings, WBC count, and lymphoblast Ia and common ALL antigen positivity). Pre-B ALL patients treated with the same treatment regimens as were null ALL patients appear to have shorter durations of complete remission, although the difference has not yet reached statistical significance. Results suggest that the male predominance and older age distribution previously recognized for E-rosette-positive T-cell leukemia can also be expected in the E-rosette-intermediate and E-rosette-negative T-cell ALL subsets, although statistically higher WBC counts at diagnosis are seen in the E-rosette-positive subset. Mediastinal mass at diagnosis is most likely in the patient with E-rosette-positive, thymocyte antigen-positive lymphoblasts. The E-rosette intermediate and E-rosette negative, as well as the E-rosette positive, T-cell ALL subsets appear to constitute poor prognosis categories. Correlation with treatment results is preliminary in all groups but suggests that stratification of ALL at diagnosis according to several immunological subgroupings may prove helpful in planning therapy. (Author abstract) (32 Refs)

25. IMMUNOLOGICAL DEFINITION OF LEUKEMIC CELL SURFACE PHENOTYPES.

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Cancer Res; 41(11,part2):4790-4793 1981

Immunological phenotyping of blasts from over 200 children with acute lymphocytic leukemia (ALL) reveals both interpatient differences and phenotypic heterogeneity in the blast population from individual patients. A battery of five independent lymphocyte differentiation markers, RBC-forming rosettes, T-cell antigens, Ia-like antigens, the common ALL antigen, and surface Ig, permit classification of all ALL specimens into four major marker groups. These are common, T-cell, B-cell, and undifferentiated ALL. Heterogeneity in the marker phenotypes within each of the major groups is observed. Within individual RBC receptor-positive ALL specimens, phenotypic heterogeneity in the blast population is demonstrated. Sequential determinations of the blast phenotype during periods of active disease reveal a second example of intrapatient blast cell heterogeneity. Differences in phenotype of the dominant blast populations present prior to treatment and at relapse are observed in sequential studies of individual patients. These shifts in phenotype are nonrandom. They result most frequently from losses in single differentiation markers. A unifying hypothesis which explains these observations of phenotypic heterogeneity is that ALL blasts manifest limited lymphoid-like differentiation. (Author abstract) (8 Refs)

26. TECHNICS FOR IMMUNODIAGNOSIS OF NON-HODGKIN LYMPHOMA (NHL) (MEETING ABSTRACT).

Malberg K, Anger G
No affiliation given
Zentralbl Allg Pathol; 125(1):74 1981

Immunologic technics complement the morphologic and cytochemical diagnosis of non-Hodgkin's lymphoma (NHL). Malignant lymphoma cells are assigned to the B-, T-, or null-lymphocyte population. In combination with the classical methods, it is possible to subclassify NHL with implications for treatment and prognosis. Specimens for study are provided by lymph nodes (biopsies, aspirates), peripheral blood cells and serum. Serum is tested for monoclonal immunoglobulin (Ig) or L-chains by means of immunoelectrophoresis or isoelectric focusing. Surface markers (membrane antigens and receptors) and cytoplasmic markers (Ig, J-chains) of malignant lymphpcytes can be determined by various immunofluorescent, immunoenzyme and rosette technics as well as the lymphocyte transformation test. Recently lymphoma cell functions, eg, Ig synthesis and secretion, have been tested in vitro. The most important immunologic markers of the chief B-cell categories of the Kiel classification were discussed. In conclusion, trends toward further development of immunodiagnosis of NHL were illustrated by means of examples. Among them are the identification of new human lymphocyte differentiation antigens by means of heterologous (hybridoma) or homologous antibodies, the search for lymphoma-specific antigens like the c acute lymphocytic leukemia antigen, and the further quantification of the functional performance of B-and T-lymphocytes. The limits of NHL immunodiagnosis were indicated. (no Refs) (In GER)

27. CLINICAL SIGNIFICANCE OF IMMUNOGLOBULIN-SECRETING CELLS IN THE PERIPHERAL BLOOD IN PATIENTS WITH MULTIPLE MYELOMA.

Nagai K, Takatsuki K, Uchino H
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Scand J Immunol; 14(2):99-108 1981

Ig-secreting cells were enumerated in the peripheral blood of 31 patients with multiple myeloma, 9 patients with so-called benign monoclonal gammopathy, and 10 patients with polyclonal hypergammaglobulinemia or idiopathic hypogammaglobulinemia. Ig-secreting cells were detected by a hemolytic plaque assay using protein-A-coated RBC in the presence of class- or type-specific rabbit anti-human Ig antisera. In about two-thirds of patients with multiple myeloma cells secreting the same light-chain isotype of their serum M-protein increased in number, whereas this was not the case in the patients with so-called benign monoclonal gammopathy. Follow-up studies of Ig-secreting cells in multiple myeloma revealed that these cells increased or decreased, correlating with the severity of the disease, and alterations were more rapid than other clinical features. This plaque assay is therefore useful in evaluating the response to chemotherapy in patients with multiple myeloma. (Author abstract) (24 Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

28. COMPARISON BETWEEN CALCITONIN AND CEA RIA IN THE MANAGEMENT OF MEDULLARY THYROID CARCINOMA (MEETING ABSTRACT).

Girelli ME, Busnardo B, Moro A, Simioni N, Scotton G
No affiliation given
Eur J Nucl Med; 6:71 1981

Serum levels of Calcitonin (CT) and Carcino Embyronic Antigen (CEA), were measured by radioimmunoassay in 35 out of a group of 46 patients with Medullary thyroid carcinoma. Sixteen patients were studied before thyroidectomy, and 19 patients only after treatment. In a total of 29 patients CT and CEA levels were repeatly evaluated by serial blood samples over a 1-4 yr period. Before operation 15 of the 16 patients showed elevated CT levels and only 10 showed elevated CEA levels. After operation 58% of the patients showed elevated CT levels and only 31% elevated CEA levels. No patient neither before nor after thyroidectomy showed elevated CEA with normal CT levels. Significant positive correlation between CT and CEA levels was found. Before operation, patients without metastases seem to have had CT and CEA levels less increased than those of patients with local or distant metastases. The difference becomes more evident after treatment. Of the 16 patients without metastases 5 had persistently elevated CT levels and 2 elevated CEA levels. Of the 12 patients with metastases 10 had elevated CT levels and 7 elevated CEA levels. Persistent elevation of CT levels after thyroidectomy in absence of evident metastases, even though CEA levels are normal, probably reflects the presence of minute occult foci of tumor, primary or metastatic. The data suggest that the production of CEA by MCT is less constant and less sensitive than that of CT, which remains the best marker of Medullary thyroid carcinoma. (no Refs)

29. SEQUENTIAL GALACTOSYLTRANSFERASE AND CARCINOEMBRYONIC ANTIGEN LEVELS IN ADVANCED BREAST CARCINOMA.

Paone JF, Baker RR, Waalkes TP, Shaper JH
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J Surg Res; 31(4):269-273 1981

UDP-galactosyltransferase (GT), an enzyme that functions in the biosynthesis of glycoproteins, has recently been found to be a sensitive biologic tumor marker. In the present study, sequential GT levels were compared to simultaneous CEA determinations to establish which biomarker more accurately reflects changes in tumor activity in patients receiving therapy for advanced breast carcinoma. Serum levels of GT and CEA were measured each mo in 38 patients undergoing combination chemotherapy for metastatic breast carcinoma. The results were correlated with the objective responses observed to chemotherapy during this period. Prior to the institution of chemotherapy, significant serum GT elevations were observed in 84.2% (32/38) of the patients, while 55.3% (21/38) had elevations in levels of CEA. During therapy 71.4% (10/14) and 50% (7/14) of the GT and CEA levels, respectively, decreased in patients who had an objective response to therapy. In the patients whose disease progressed on therapy, 75% (18/24) had significant increases in GT levels during this interval, while 41.6% (10/24) had increases in CEA (p less than 0.01). Furthermore, in 11 patients (29.5%) serum GT alterations correctly reflected changes in tumor activity, while CEA levels remain static. These data indicate that GT is more sensitive than CEA as a marker for breast carcinoma and suggest that GT may be clinically useful in the management of patients with metastatic breast disease. (Author abstract) (21 Refs)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

30. BETA2-MICROGLOBULIN IN CANCER.

Pesce AJ, Weiss MA, DiPersio L, Michael JC
Univ. Cincinati Medical Center, Cincinati, OH
IMJ; 160(3):191-195 1981

Early discovery of the role of beta2-microglobulin (B2m) in cancer is reviewed along with results of various studies. Human B2m was readily identified and quantified in the plasma of athymi c mice bearing various human tumors, and the amount in the plasma was directly related to the amount of B2m in tumor extracts. The level of B2m varied widely and was lowest in tumors with the fastest growth rate. Immunofluorescence studie in individual tumor cells showed wide variations in B2m content; some poorly differentiated carcinomas exhibited no B2m. Studies of mouse teratocarcinoma cell lines support the concept that B2m may be a marker of differentiation in cells. Since B2m forms parts of the human histocompatibility antigens, it may serve as a marker for these antigens. Data indicate serum level of B2m can be used to mark cancer if the tumor cells produce large amounts as in lymphoproliferative disorders. A potentially more important use of this marker is in immunohistology, where it might be used to characterize tumor differentiation, heterogeneity, and metastatic capacity.

31. INVESTIGATION OF MEASURING PREGNANCY-SPECIFIC BETA-GLYCOPROTEIN (SP1) IN NONTROPHOBLASTIC MALIGNANT TUMOR.

Tsujino D, Sasaki Y, Fukushima M, Someya K, Saito K
Third Dept. Internal Medicine, Saint Marianna Univ. Sch. Medicine, Kawasaki, Japan
Gan No Rinsho; 27(11):1355-1358 1981

Concentrations of SP1 in the plasma, abdominal ascites or pleural effusion, and the tumor tissues of 187 patients with nontrophoblastic tumors and 80 patients with benign diseases were measured with the radioimmunoassay-gnost SP1 kit. SP1-positive tests were observed in the plasm of 4/32 patients with stomach cancer, 3/30 with colorectal cancer, 1/19 with uterine cancer, 4/18 with liver cancer, 1/15 with ovarian cancer, 1/10 with esophageal cancer, and 1/5 with testicular cancer. Overall, 15/187 patients had plasma SP1-positive tests in concentrations of 3-1,390 nanog/ml, and 2/30 control patients with benign diseases had plasma SP1-positive tests in concentrations of 3 and 18 nanog/ml, respectively. Because the SP1-positive rates were the same for the cancer and benign disease patients, and because the levels of plasma SP1 were not consistent throughout the course of the disease in the cancer patients, the SP1-plasma test was thought to have low clinical diagnostic value. SP1 was detected in the pleural effusion and abdominal ascites 3/26 and 1/16 cancer patients, respectively, but was not detected in the control patients. SP1 was detected in the tumor tissue of 2/5 cancer patients. Plasma SP1 was not thought to be a useful tumor marker for patients with non-trophoblastic tumors. (11 Refs) (In JPN)

32. ALTERATIONS OF PLASMA FIBRINOGEN LEVELS IN MALIGNANT LYMPHOMA.

Opat P, Rejthar A, Tomanova J, Trnka A, Wotke R
Res. Inst. Clinical and Experimental Oncology, 602 00 Brno, Czechoslovakia
Neoplasma; 28(3):339-343 1981

Fibrinogen levels were investigated in the plasma of a group of patients with ma lignant lymphoma consisting of M Hodgkin's and non-Hodgkin's lymphoma, and were found to be significantly higher in an acute onset of the disease and in relapses, than in a control group of healthy blood donors. In the terminal stages, fibrinogen levels in the plasma were observed to decline towards the upper normal limits. Plasma fibrinogen levels are considered to be a good indicator of the activity of the disease. (Author abstract) (16 Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

33. TRANSFORMATION ASSOCIATED FETAL ANTIGENS IN HUMAN PREMALIGNANT COLONIC EPITHELIAL CELLS (MEETING ABSTRACT).

Higgins PJ, Friedman E, Lipkin M, Hertz R, Attiyeh F
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Gastroenterology; 80(5,part2):1174 1981

Premalignant and malignant colonic cells were analyzed for transformation associated fetal antigens by immunohistologic techniques using rabbit antiserum to combined saline extracts of heart, lung, liver, kidney, spleen and small and large intestine obtained from a 2nd trimester human abortus. Antiserum had been absorbed with extracts of the corresponding adult tissues obtained at autopsy from non-cancer related deaths, and A and B RBC. Immunohistologic studies revealed anti-fetal reactivity in 84% of colonic adenocarcinomas examined by cryostat sectioning, and in all established and short term colon carcinoma cell cultures tested. Normal epithelial cells of the colon did not stain with this anti-serum. Absorption of anti-2nd trimester fetus serum with an established colon carcinoma cell line (SW 1116) removed anti-body to all tumors. Parallel absorptions with extracts of normal colonic tissues were without effect, suggesting that the anti-serum recognizes one or several closely related fetal antigens. Control experiments indicated that the antigen(s) detected was not alpha fetoprotein, beta human chorionic gonadotropin, or carcinoembryonic antigen. Primary cultures of adenomatous colonic epithelial cells were then examined for the presence of fetal antigen. Cultured epithelial cells stained positively in 2 of 11 (18%) tubular adenomas, 3 of 6 (50%) villotubular adenomas, and 5 of 6 (83%) villous adenomas. We conclude that colonic epithelial cells of human adenomas express fetal antigen with increased frequency as they progress through stages towards frank carcinoma. (no Refs)

34. GLYCOPROTEIN DEGRADING GLYCOSIDASES IN EXPERIMENTAL CANCER OF THE COLON (MEETING ABSTRACT).

Prizont R, Piatt K
Department of Medicine, Albuquerque Veterans Administration Medical Center, Albuquerque, NM
Gastroenterology; 80(5,part2):1255 1981

In this study, we have investigated the non-blood group degrading beta-Galactosidase (beta-Galase) and beta-N-Acetylglucosaminidase (beta-Glnase) in experimentally induced colonic can cer. Ten Wistar rats (ER) were injected for 10 wk with 25 mg/kg of 1,2 dimethylhydrazine (DMH) and fed a diet containing casein (20%), sucrose (50%), fat (5%) and cellulose fiber (5%). Another group of 10 rats (EHF) were similarly injected with DMH but the aforementioned diet was modified by both an increase in cellulose (to 15%) and a decrease in sucrose (to 40%). Two groups of rats, 6 each, were injected with buffer and served as controls for regular (CR) or high fiber (CHF) diets. Feces were collected, homogenized in saline and centrifuged to sediment the bacteria. Bacteria free supernatants were then used for analytical assays against p-nitro-phenylglycosides. When control and experimental animals were compared by diet (CHF vs EHF, CR vs ER), no significant differences in the enzyme levels were found. When animals were sacrificed 7 mo post-initial injection, significantly more tumors were recovered from large and small bowels of ER animals than were recovered from small bowels of EHF rats. This study suggests that high cellulose diets significantly decrease production of fecal non-blood group degrading glycosidases. (2 Refs)

35. PLASMINOGEN ACTIVATOR: A MARKER FOR HUMAN PROSTATIC EPITHELIUM AND PROSTATE CANCER (MEETING ABSTRACT).

Webber MM, James G, Lucero L, Van Buskirk JJ, Wettlaufer JN
Divisions of Urology and Neurosurgery and Department of Neurology, University of Colorada Health Sciences Center, Denver, CO, 80262
In Vitro; 17(3):249 1981

Secretion by prostatic epithelium of a plasminogen activator (PMA), which is involved in the liquefaction of semen, is an expression of differentiated function. Our studies are directed towards the isolation, characterization and quantitation of a human prostate-specific PMA which may be used as (a) a marker for prostatic epithelium in culture; (b) an indicator of the stage of prostate cancer and (c) an indicator of the efficacy of treatment. Fibrinolysis using fibrin agar overlay and caseinolysis were used to detect PMA. Samples of sperm-free seminal plasma, cryoprecipitated seminal plasma and culture medium from prostate carcinoma cultures gave a strong positive, medium from adult prostate epithelial cultures a weak positive, and that from mouse melanoma cell line B-16 a negative response. Urokinase and PBS were used as known positive and negative controls. The activity of PMA was found to be plasminogen-dependent since no reaction occurred in the absence of serum. PMA activity in conditioned medium from prostate carcinoma cell lines is being investigated. This in vitro cell system using PMA, a secretory product, is ideal for studying regulation of growth and differentiation in vitro. (no Refs)

36. TERMINAL DIFFERENTIATION SURFACE ANTIGENS OF MYELOMONOCYTIC CELLS ARE EXPRESSED IN HUMAN PROMYELOCYTIC LEUKEMIA CELLS (HL60) TREATED WITH CHEMICAL INDUCERS.

Perussia B, Lebman D, Ip S H, Rovera G, Trinchieri G
Wistar Inst. Anatomy and Biology, 36th and Spruce St., Philadelphia, PA, 19104
Blood; 58(4):836-843 1981

The expression of two surface antigens present on the cell membrane of both human granulocytes and monocytes was studied during the process of myelomonocytic differentiation using two monoclonal antibodies (B9.8.1 and B13.4.1). These surface antigens are not present on immature myeloid cells nor on nonmyeloid hematopoietic cells, but can be detected when

the cells are terminally differentiated. Among the bone marrow cells, B13.4.1 binds to metamyelocytes and B9.8.1 to metamyelocytes and a fraction (30%) of myelocytes. HL60 human promyelocytic leukemia cells did not react with such monoclonal antibodies. However, when such cells were induced to differentiate in vitro into mature myeloid elements by treatment with retinoic acid or dimethyl sulfoxide, 70%-90% of the differentiated cells expressed both surface antigens. Cell sorting studies on these treated HL60 cells indicated that myelocytes and metamyelocytes were the most immature cells expressing such markers. Expression of the two surface antigens was also observed when HL60 cells were induced to differentiate into monocyte/macrophage cells by treatment with the tumor promoter 12-0-tetradecanoyl-phorbol-13-acetate. Thus, human promyelocytic leukemia cells induced to differentiate in vitro by treatment with specific chemical agents express membrane antigens in the same pattern as normal bone marrow myeloid cells at the corresponding stage of differentiation. (Author abstract) (26 Refs)

37. RECEPTOR MEDIATED MURINE LEUKEMOGENESIS: MONOCLONAL ANTIBODY INDUCED LYMPHOMA CELL GROWTH ARREST.

McGrath MS, Jerabek L, Pillemer E, Steinberg RA, Weissman IL
Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA, 94305
Haematol Blood Transfus; 26:360-364 1981

A receptor-mediated leukemogenesis hypothesis that T lymphocytes are clones of T cells bearing mitogen-linked surface receptors specific for the envelope determinants of the inducing murine leukemia virus was tested. Experiments examined the central postulate that continued leukemic proliferation is the result of continued antigenic stimulation of T lymphomas. Monoclonal antibody reagents to leukemia cell surface determinants were raised; the effect of these antibodies was tested on leukemic cell proliferation in vitro and on specific virus binding to the cells. Several antibodies which inhibited lymphoma cell proliferation in vitro were found. Evidence is presented that inhibition may be due to a blockade in virus binding to these cells. (17 Refs)

38. EXPRESSION OF THE OKT MONOCLONAL ANTIBODY DEFINED ANTIGENIC DETERMINANTS IN MALIGNANCY.

Greaves M, Delia D, Sutherland R, Rao J, Verbi W, Kemshead J, Hariri G, Goldstei n G, Kung P
Membrane Immunology Lab., Imperial Cancer Res. Fund, London WC2A 3PX, England
Int J Immunopharmacol; 3(3):283-299 1981

Cellular specificity in human leukemia of murine monoclonal antibodies OKT1, 3, 4, 6, 8, 9, 10, 11, and 11A were screened by microscopic and flow cytometric immunofluorescence methods and 125I-binding assays. Tests against malignant T cells showed a correlation between phenotype and clinical diagnosis. T cells from acute lymphoblastic leukemia (T-ALL) cells always showed an immature phenotype. Non-Hodgkin T lymphoma cells showed a cortical thymic phenotype. Both cell types appear to originate from T cell precursors. Cells from chronic T leukemias and cutaneous T lymphomas and leukemias that occur primarily in older adults showed mature T cell phenotypes. OKT11 and OKT11A reacted similarly with sheep E rosettes and appear to react to the same structures. Several T-ALL cell lines were modified in vitro to a more mature phenotype by 12-O-tetradecanoylphorbol 13 acetate or other inducers. This was demonstrated by binding of OKT1, 8, 9, 11, and other antibodies. OKT9 reacted preferentially with T leukemias, but was not T-specific, binding also to other leukemia cells and to other malignant tumor types. Cells induced to mature in vitro lost the OKT9 determinant. OTK9 bound to a receptor that may be a marker for malignancy. OKT10 bound to leukemias and normal bone marrow cells of the myeloid and B cell lineages. OTK6 bound to neuroblastoma cells. (43 Refs)

39. LYMPHOCYTES MAINTAINED IN T-CELL GROWTH FACTOR (INTERLEUKIN 2) SHOW ENHANCED CYTOTOXICITY FOR HUMAN TUMOUR CELLS (MEETING ABSTRACT).

Vose BM, Moore M
Christie Hospital and Holt Radium Institute, Manchester M20 9BX, England
Br J Cancer; 43(5):724 1981

Conditions for the production of supernates from mitogen-stimulated human lymphocytes with the capacity to induce proliferation in long-term mixed lymphocyte culture (MLC) or phytohemagglutinin (PHA) cultures which do not respond to PHA have been investigated. These supernates can be used to maintain lymphocytes in continuous growth with a doubling time of approx 48 hr. Cells grown from MLC-stimulated cultures show greater than 80% sheep RBC-rosetting cells, are Fc-, do not show antibody dependent cellular cytotoxicity activity and have reduced lysis of K562 compared with freshly isolated effectors. Cultured T cells (CTC) show high lytic activity against the inducing PHA blasts but not against autologous or third-party targets. Similar experiments have been performed with lymphocytes from the blood, lymph node, spleen and tumor of cancer patients, and CTC tested for cytotoxicity against autologous and allogeneic tumor cells and the K562 cell line. Cytotoxicity for autologous tumor was found in all samples. This was accompanied by killing of allogeneic cells in most instances, but killing of K562 was only rarely demonstrable. These data would be consistent with a polyclonal expansion of cytotoxic effectors in the samples. The finding of autologous reactivity suggests the presence of autorecognitive cytotoxic T cells in cancer patients with specificity for tumor. (no Refs)

40. GALACTOSYL SPECIFIC RECEPTOR ON LIVER CELLS: BINDING SITE FOR TUMOR CELLS.

Schlepper-Schafer J, Friedrich E, Kolb H
Institut fur Biophysik und Elektronenmikroskopie der Universitat, Moorenstr. 5, D-4000 Dusseldorf 1, W. Germany
Eur J Cell Biol; 25(1):95-102 1981

In this paper the recognition of various rat tumor cells by rat liver cells is demonstrated in vitro. A liver cell receptor involved in the binding process has been identified. The ultrastructure of the cell contacts was examined by transmission electron microscopy. Hepatocytes and Kupffer cells were isolated from rat liver by collagenase treatment and cell adhesion tests were performed with four different tumor cell types. Hepatocytes were found to bind Walker sarcoma cells, lymphoma cells and Yoshida hepatoma cells but not leukemia 5222 cells. Kupffer cells bound all tumor cell types. Normal blood cells were not bound under the same conditions. Recognition of tumor cells by hepatocytes was mediated by a galactose specific lectin on the liver cell surface as shown by hapten inhibition experiments with specific saccharides. Although Kupffer cells express a similar lectin-like receptor adhesion of tumor cells, they could not or could only slightly be inhibited by galactose or related saccharides. It is concluded that the spontaneous adhesion of tumor cells to liver cells in vitro is a specific recogni-

tion event which in part is mediated by lectin-carbohydrate interactions. (Author abstract) (33 Refs)

41. EXPERIMENTAL CARCINOMA OF THE COLON: SERUM HAPTOGLOBIN IN EARLY DIAGNOSIS (MEETING ABSTRACT).

Amiguet JA, Munoz-Navas M, Conchillo F, Ortiz de Landazuri E, Liso P
Department of Medicine, University Clinic, University of Navarra, Pamplona, Spain
Gut; 22(5):A444 1981

Haptoglobin has shown its usefulness in the biological diagnosis of colon cancer. The possible interest of this protein indicator for purposes of early diagnosis motivated this experiment. The weekly administration of 40 mg/kg wt of 1,2 dimethylhydrazine to Wistar rats produced early neoplastic lesions from the 15th wk. Haptoglobin was quantified by simple radial immuno-diffusion against a specific immunoserum anti-human haptoglobin 1-1, obtained by us through an original technique. This antiserum had been previously used in measuring haptoglobin in experimental hepatoma of the rat. This subtype haptoglobin 1-1 possesses crossed antigenicity with the rat variety. Early histological lesions coincided with a s tatistically significant rise of haptoglobin in serum. The cause of haptoglobin serum increase in neoplasms is still unknown. In conclusion, we have found that haptoglobin is a useful biological marker in early carcinoma of the colon. (no Refs)

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. LOCALIZATION OF EARLY RECURRENCE OF CARCINOMA OF THE COLON OR RECTUM BY RADIOIMMUNODETECTION IN PATIENTS WITH A RISING SERUM CARCINOEMBRYONIC ANTIGEN CONCENTRATION (MEETING ABSTRACT).

Begent RH, Keep PA, Searle F, Dent J, Bagshawe KD, Jones BE, Jewkes RF, Vernon P
Department of Medical Oncology, Charing Cross Hospital, London, W6 8RF, England
Oncodev Biol Med; AbstractsBook,1:P62 1981

Radioimmunodetection (RID) for localization of carcinoma of the colon or rectum by external scintigraphy after injection of 131 Iodine labelled antibody to carcinoembryonic antigen (CEA) has been reported. The purpose of this study was to investigate whether the method could be used to localize recurrence of carcinoma of the colon and rectum which have been predicted by rises in concentration of serum CEA during follow-up after apparently curative resection. RID was performed using the method of Goldenberg in 10 patients with raised serum CEA in the absence of symptoms or physical signs of recurrence. RID was positive in 9, the sites being liver alone, 3; liver and para-aortic nodes, 1; liver and retrovesical area, 1; liver and colon, 1; perineum, 1; bone, 1; para-colic area, 1. These recurrences have been confirmed unequivocally in 4 patients. While recurrence is likely in the remaining 5 patients it has not been definitely demonstrated by conventional radiology or surgery. These preliminary data suggest that RID may be useful in the investigation of patients in whom subclinical recurrence of carcinoma of the colon or rectum is suspected. In its present form it can be used to indicate which sites of suspected recurrence should be further investigated. (1 Ref)

2. PREOPERATIVE SERUM CEA CONCENTRATION AND CLINICAL STAGING AS PROGNOSTIC FACTORS IN COLORECTAL CANCER (MEETING ABSTRACT).

Staab HJ, Brummendorf T, Anderer FA
Friedrich-Miescher-Institut, Max-Planck-Gesellschaft, Tubingen, W. Germany
Oncodev Biol Med; AbstractsBook,1:61 1981

Most of the earlier investigations on the prognostic value of the preoperative serum carcinoembryonic antigen (CEA) concentration in cancer patients examined its correlation with disease recurrence. In this report observed survival time was computed for 563 patients registered for resection of colorectal cancer since 1974. Significant difference in the survival rate was found for patients with different resectability, with different tumor extension and with different ranges of preoperative serum CEA concentrations. In addition, preoperative CEA concentration represented a significant gain in prognostic information within groups of patients with distinct resectability or/and tumor extension. The results indicated strongly that the preoperative serum CEA concentration seems to be an independent prognostic criterion within a group of clinically defined patients with comparable resectability and identical tumor, node, metastasis classification of their tumors. Therefore preoperative CEA determination, which can be established within about 10 days during hospitalization for primary treatment, should be included in clinical methods to give further information on patients with high risk. (no Refs)

3. THE USE OF CEA IN THE JAUNDICED PATIENT: DIAGNOSIS, STAGING, FOLLOW-UP, PROGNOSI S (MEETING ABSTRACT).

Martin EW, Strah K, Ferrara J, Martin DT, Cooperman M
The Department of Surgery, The Ohio State University College of Medicine, Columbus, OH, 43210
Newsletter Natl Pancreas Cancer Project; VI(2):39 1981

Preoperative plasma carcinoembryonic antigen (CEA) levels were determined by Roche Assay in 100 jaundiced patients, 78 with malignant disease and 22 with benign disease. Levels were above 4.0 ng/ml in 50 of 54 (92.6%) with pancreatic cancer, 15 of 18 (83.3%) with cholangiocarcinoma, 3 of 4 (75%) with ampullary cancer, and 1 of 2 (50%) with gallbladder cancer. Only 4 of 22 patients (18%) with benign disease had levels above 4.0 ng/ml. A preoperative CEA above 10.0 ng/ml was even more significant; no patient with benign disease had values over 7.5 ng/ml. On the contrary, 30 of 78 patients with proved malignant disease who had CEA levels above 10 ng/ml had unresectable tumors, and only 3 are living. Preoperative CEA values are helpful to the surgeon as an indication of resectability of tumor and to all clinicians in arriving at a realistic prognosis. Serial CEA determinations have proved useful in following the progression of the disease and in evaluating treatment. (no Refs)

4. CARCINOEMBRYONIC ANTIGEN: A USEFUL MONITOR OF THERAPY OF SMALL CELL LUNG CANCER.

Goslin RH, Skarin AT, Zamcheck N
(c/o Skarin) Medical Oncology Div., Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
JAMA; 246(19):2173-2176 1981

In 85 patients with small cell cancer of the lung, the degree of carcinoembryonic antigen (CEA) elevation correlated with the extent of disease. Normal CEA levels (less than 2.5 ng/mL) occurred in 55% of patients with limited disease compared with 12% of patients with extensive disease. All patients with CEA levels greater than 50 ng/mL had liver involvement. Serial CEA levels were useful in monitoring response to chemotherapy and in predicting relapse. All patients with CEA values greater than 5.0 ng/mL before start of treatment had a fall in CEA level with response to treatment and a rise in CEA level when resistance to chemotherapy developed. In patients with CEA levels of less than 5.0 ng/mL at the start of treatment, rising values reflected the onset of recurrent disease in 10 of 21 patients who had relapses. The CEA levels used in conjunction with standard roentgenograms and organ scanning studies can aid in the initial staging of small cell cancer of the lung, and in monitoring treatment. (Author abstract) (26 Refs)

5. IMMUNOPEROXIDASE STAINING FOR CARCINOEMBRYONIC ANTIGEN IN SMALL CELL CARCINOMA OF THE LUNG.

Sehested M, Hirsch FR, Hou-Jensen K
Dept. Pathological Anatomy, Herlev Hosp., Univ. Copenhagen, DK-2730 Herlev, Denmark
Eur J Cancer Clin Oncol; 17(10):1125-1131 1981

Diagnostic pretreatment biopsies in 53 patients with small cell carcinoma of the lung (SCCL) were examined retrospectively for presence of carcinoembryonic antigen (CEA). The unlabeled antibody-enzyme (PAP) technique was utilized. All patients had been treated with intensive chemotherapy. The patients were divided into three groups according to the immunoperoxidase staining reactions of the biopsies. Thirteen

(24.5%) patients had biopsies that were strongly positive for CEA while 22 (41.5%) had slightly positive and 18 (34%) had negative biopsies. The patients with biopsies strongly positive for CEA had a significantly longer survival as compared with patients with negative staining results (p less than 0:05). No significant correlation was observed between immunoperoxidase staining for CEA and morphological subtypes of SCCL according to the WHO 1977 classification. (Author abstract) (15 Refs)

6. CLINICAL SIGNIFICANCE OF MEASUREMENTS OF CARCINOEMBRYONIC ANTIGEN IN SERUM OF PATIENTS WITH CARCINOMA OF THE UTERINE CERVIX.

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Arch Gynecol; 230(4):263-273 1981

Serum carcinoembryonic antigen (CEA) levels were measured in 108 patients suffering from carcinoma of the uterine cervix before and immediately after treatment. Follow-up was extended for up to 990 days. In 88 of these patients (age 33-80 yr), the CEA levels were determined serially beginning with detection of the disease. In 20 patients (age 40-80 yr) the study was begun when diagnosis of recurrent disease was made. Three patients with stage Ib disease were treated by radical hysterectomy and pelvic lymphadenectomy. The remaining patients were treated with combined radiation therapy consisting of local application of radium 2-3x with a total dose of up to 5,200 mgeh and external radiation. A total dose of 40 Gy2 was given to the parametrium through two anterior and posterior portals. The highest value of CEA measured in a control group of healthy subjects was 12 nanog/ml. Of 88 patients with cervical carcinoma, 38 had values greater than 12 nanog/ml. Positive correlation could be made between elevated CEA and clinical stage of disease. CEA level before treatment was not prognostic for survival, but level after therapy indicated median survival time. (19 Refs)

7. RELATIONSHIP BETWEEN SERUM ALPHA-FOETOPROTEIN, CIRRHOSIS AND SURVIVAL IN HEPATOCELLULAR CARCINOMA.

Johnson PJ, Melia WM, Palmer MK, Portmann B, Williams R

Liver Unit, King' Coll. Hosp. Medical Sch., Denmark Hill, London SE5, England

Br J Cancer; 44(4):502-505 1981

An analysis of survival time of 57 West European patients with hepatocellular carcinoma was carried out to define which of several possible factors (age, sex, cirrhosis and raised serum alpha-fetoprotein (AFP)) influenced survival. Although survival was significantly longer in younger patie nts (p less than 0.02) and in patients with normal serum AFP (p less than 0.01), multivariate analysis showed that significant variation in survival time is better explained by the single factor, the presence of cirrhosis, than by AFP level. This does not seem to apply for patients with this tumor in Africa and the Far East, and there may be a fundamental difference in the natural history of the tumor between high- and low-incidence areas. (Author abstract) (14 Refs)

8. AFP IN YOLK SAC TUMOR AND SOLID TERATOMA OF THE OVARY: SIGNIFICANCE OF POSTOPERATIVE SERUM AFP.

Ishiguro T, Yoshida Y, Tenzaki T, Ohshima M, Suzuki H

Dept. Obstetrics and Gynecology, Shiga Univ. Medical Science, Seta, Ohtsu 520-21, Japan

Cancer; 48(11):2480-2484 1981

Serial serum alpha-fetoprotein (AFP) was examined postoperatively in five patients with yolk sac tumor and in three with solid teratoma of the ovary. Serial estimation of AFP was also done in sera from postpartum patients to compare the decreasing ratio between the two groups. Serum AFP in these postpartum women decreased according to the exponential function curve as AFP = be-mx (x = days after delivery) with a mean m value of 0.1652 and a mean correlation coefficient of-0.9911. Half-time of serum AFP in postpartum subjects was 4.33 days. Exponential decrease of serum AFP was also found in postoperative patients with yolk sac tumor and solid teratoma of the ovary. However, in those in whom there was an incomplete removal of the tumors, the values of either m or coefficient of correlation were significantly lower as compared to those in patients with complete extirpation of lesions or those in postpartum subjects. Elevation of serum AFP was noted postoperatively in two patients with recurrences; however, significant decreases in AFP following chemotherapy were apparent in one patient with immature solid teratoma. These findings suggest that the decreasing ratio of postoperative serum AFP is an effective indicator to determine whether or not the lesions were completely extirpated, although a normal value may not always imply the absence of microscopic metastasis of tumor cells. Serial estimation of serum AFP was of value in assessing the presence of recurrences and evaluating the efficacy of chemotherapy. (Author abstract) (12 Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

9. COMPARISON OF PROSTATIC ACID PHOSPHATASE ASSAYS.

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Arch Pathol Lab Med; 105(11):622-625 1981

A prospective study compared five different assays for serum prostatic acid phosphatase in the detection of carcinoma of the prostate gland. The assays included two radioimmunoassay procedures, one counterimmunoelectrophoresis procedure, and an enzymatic procedure using alpha-n aphthol phosphate substrate with and without sodium tartrate inhibition. The patients' hospital records were reviewed, as were all available surgical histology slides. The patients were divided into four groups: prostatic carcinoma, benign prostatic hypertrophy, other carcinomas (besides prostatic carcinoma), and no related disease states (that would be expected to give elevated acid phosphatase levels). The results were analyzed with respect to sensitivity, specificity, predictive values of a positive result, predictive value of a negative result, and efficiency of the assays. (Author abstract) (4 Refs)

10. AN IMMUNOPEROXIDASE TECHNIQUE TO AID IN THE DIFFERENTIAL DIAGNOSIS OF PROSTATIC CARCINOMA.

Fishleder A, Tubbs RR, Levin HS
Dept. Pathology, Cleveland Clinic, Cleveland, OH
Cleve Clin Q; 48(3):331-335 1981

The unlabeled immunoperoxidase technique and antibody to human prostatic acid phosphatase was used to study a variety of normal and neoplastic tissues. The technique was found to be a useful adjunct in the differential diagnosis of prostatic carcinoma versus transitional cell carcinoma of the bladder and rectal adenocarcinoma, but was not entirely specific, a cross-reactivity with rectal carcinoid tumors was documented. This study emphasizes the importance of controlled testing of these antibodies by pathology laboratories using immunoperoxidase techniques to assure accurate surgical pathologic diagnosis. (Author abstract) (5 Refs)

11. A PRELIMINARY STUDY OF THE CREATINE KINASE BB ISOENZYME AS A TUMOR MARKER (MEETING ABSTRACT).

Fritsche HA, Wertlake SE
Department of Laboratory Medicine, University of Texas System Cancer Center, M. D. Anderson, Hospital Houston, TX, 77030
Oncodev Biol Med; AbstractsBook,1:P15 1981

We have used a radioimmunoassay (RIA) procedure to measure the BB isoenzyme of Creatine Kinase (CK-BB) in the serum of patients with cancer. The normal range for the assay was established in a study of 170 blood donors. The upper limit of normal for CK-BB was 8.0 ng/ml and no effect of age or sex on the normal range was observed. Serum CK-BB levels were determined in 355 cancer patients with a variety of neoplastic diseases who were in various stages of their disease. Serum CK-BB elevations were frequently observed in patients with adenocarcinoma of the gastrointestinal (GI) tract, breast and prostate. Approx 50% (10/24) of the patients with GI tract malignancy undergoing therapy and 30% (6/18) patients with breast cancer had elevated serum CK-BB levels. Elevations of CK-BB in patients with prostate cancer appeared to correlate with the presence of metastatic bone disease. CK-BB elevations by RIA were confirmed by electrophoretic studies. Serial determinations of CK-BB in patients undergoing therapy correlated with the clinical response to therapy and elevations of serum CK-BB in disease free patients signaled recurrence of the disease. Borderline elevations of CK-BB (8.0-10.0 ng/ml) were observed in some cancer patients with renal failure and drug induced cardio-toxicity. These preliminary studies suggest that the CK-BB test may be useful in the clinical management of patients with cancer. (no Refs)

12. DETECTION OF TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE IN LEUKEMIA/LYMPHOMA BY AN IMMUNOENZYMATICAL ASSAY (MEETING ABSTRACT).

Hecht T, Forman SJ, Santos S, Bross KJ, Schmidt GM, Blume KD
Department of Hematology and Bone Marrow Transplantation, City of Hope National Medical Center, Duarte, CA, 91010
Exp Hematol; 9(Suppl9):12 1981

Terminal deoxynucleotidyl transferase (TdT) is now known to be an important marker for the classification of leukemias and certain types of lymphoma. Thus, much interest exists in the development of fast and sensitive tests to allow screening for the presence of TdT. A modified peroxidase-anti-peroxidase (PAP) 'sandwich' technique was used to detect TdT in peripheral WBC. To establish the value of this new test, samples from twelve patients with different hematologic diseases were tested in a blinded study with this method and the traditional tests, an immunofluorescence (IF) and a biochemical enzyme assay. One hundred percent concordance between the three methods was found in all cases studied. Moreover, the proportion of positive cells was almost higher with our new procedure when compared with the IF technique. Since the PAP technique is fast, sensitive and the reaction product stable indefinitely, we conclude that the new method may be useful in screening of all leukemia and lymphoma patients for TdT activity. (no Refs)

13. A SIMPLE TEST FOR THE TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE USING THE PEROXIDASE-ANTIPEROXIDASE TECHNIQUE.

Jager G
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Blut; 42(4):259-261 1981

A technique for detection of terminal deoxyribonucleotidyl transferase (Tdt), an enzyme marker for classification of acute lymphoblastic leukemias (ALL), is described. Cells of the Reh cell line were analyzed on a single-cell basis by the unlabeled antibody enzyme method. Mononuclear blood cells were used as controls. Results were compared with those from the immunofluorescence method. Incubation of slides at 37 C for 60 min followed by washing for 1 hr produced optimum results, with 83% of Reh cells being TdT-positive. No positive mononuclear cells or background staining were found under these conditions. The method tested offered the advantages of simplicity of necessary equipment, permanence of cell preparations, and the opportunity of counterstaining for morphological differentiation and quantitatio n of reaction product at the single-cell level. The method is recommended for routine classification of ALL. (5 Refs)

14. THE VALUE OF SERUM 5'-NUCLEOTIDE PHOSPHODIESTERASE ISOZYMES IN THE DIAGNOSIS OF PRIMARY LIVER CANCER.

Lu H, Chen Q, Jiang K, Ming D, Shi B, Ding C, Pan L, Yu J, Liu Z
Shanghai Second Medical Coll., Affiliated Xinhua Hosp., Shanghai, People's Republic of China
Zhonghua Yixue Zazhi; 60(4):219-221 1981

The use of alpha fetoprotein (AFP) determination has greatly increased the diagnostic level of primary liver cancer in recent yr. However, there is a small proportion of liver cancers that are negative for AFP. The value of serum 5'-nucleotide phosphodiesterase isoenzymes (NPI) in the diagnosis of liver cancers is described with special reference to those negative for AFP. Of 95 cases of primary liver cancer tested between 1979 and 1980, 79 cases (83.2%) were positive for NPI. Among 70 AFP-positive cases, 60 cases (85.7%) were NPI-positive and among 25 AFP-negative cases, 19 cases (76.0%) were NPI-positive. Among 15 resected cases of primary liver cancer only 2 cases (13.3%) were NPI-positive. Liver cirrhosis and HBSAG-positive hepatitis had a positive rate of 10.3% (4/39) while none of the 76 normal subjects tested was positive for NPI. It was concluded that NPI determination when combined with AFP determination is useful in the diagnosis of primary liver cancer as well as in its differential diagnosis from non-cancerous liver diseases. (7 Refs) (In CHI)

15. FURTHER INVESTIGATION OF A NOVEL GAMMA-GLUTAMYL TRANSPEPTIDASE IN HUMAN RENAL CARCINOMA (MEETING ABSTRACT).

Hada T, Higashino K, Okochi T, Yamamoto H, Sumikawa H
The Third Department of Internal Medicine, Osaka University Hospital, 1-1-50 Fukushima, Osaka 553, Japan
Oncodev Biol Med; AbstractsBook,1:51 1981

A novel gamma-glutamyl transpeptidase (GGTP) found in human renal carcinoma was reported in our previous paper. In the present study, we further investigated some enzymic and immunological properties of the novel GGTP. 1) On isoelectric focusing in sucrose density gradient, the novel GGTP was more acidic than the normal kidney enzyme. But after neuraminidase treatment, both enzymes shifted to a more alkaline range and showed a similar pattern. 2) More than 90% of normal kidney GGTP activity passed through concanavalin A (Con A) sepharose column, while that of the novel one was about 60%. After neuraminidase treatment of both enzymes, about 80% of the normal kidney GGTP still passed through Con A-sepharose column, but the novel GGTP bound to Con A-sepharose column in about 75% of its total activity. 3) The inhibition patterns of both normal kidney GGTP and the novel one by anti-normal kidney GGTP antibody were almost the same. In an Ouchterlony double diffusion test the precipitin lines of the novel GGTP and the normal kidney agai nst anti-normal kidney GGTP antibody fused completely. These data may indicate that the novel GGTP is immunologically identical with the normal kidney enzyme, but that it differs from the latter at least in its sialic acid content and in some other carbohydrate moieties. (no Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

16. ESTROGEN RECEPTOR QUANTITATION AND STAGING AS COMPLEMENTARY PROGNOSTIC INDICATORS IN BREAST CANCER: A STUDY OF 583 PATIENTS.

Godolphin W, Elwood JM, Spinelli JJ
Div. Clinical Chemistry, Vancouver General Hosp., Vancouver, B.C., Canada
Int J Cancer; 28(6):677-683 1981

Estrogen receptor (ER) quantity was measured at the time of primary diagnosis on 583 patients with breast cancer seen at the major treatment center in British Columbia between 1975 and 1979. Survival rates (overall, recurrence-free and post-recurrence) were assessed relative to ER concentration, staging, menopausal status, age, differentiation, and therapy. A linear trend in increased survival was demonstrable through variations in ER concentration from less than or equal to to greater than or equal to 260 fmoles/mg cytosol protein. This trend was highly significant and remained after adjustment for stage, menopausal status, and age, and was seen for all groups of patients except those with metastatic disease. The association of high ER concentration with increased recurrence-free survival was not due to differing response to adjuvant therapy, but the trend in post-recurrence survival was only significant in patients who had received hormonal therapy. Survival was as strongly associated with receptor concentration as with staging, and these two factors were almost completely independent. A proportional hazards model was fitted to produce predictions of survival, and showed that TNM Stage III patients with high ER concentrations have a better survival than Stage I or II patients with lower ER concentrations. This suggests that quantitative assessment of ER status is essential to definition of risk in breast cancer patients and that stratification in clinical trials and consideration for adjuvant therapy ought to be guided, in part, by a standardized ER-quantitative determination performed on the primary tumor. (Author abstract) (34 Refs)

17. CORRELATION OF ESTROGEN RECEPTORS AND RESPONSE TO CHEMOTHERAPY OF CYCLOPHOSPHAMIDE, METHOTREXATE, AND 5-FLUOROURACIL (CMF) IN ADVANCED BREAST CANCER.

Chang JC, Wergowske G
Good Samaritan Hosp. and Health Center, Dayton, OH, 45406
Cancer; 48(11):2503-2506 1981

Thirty-six patients with advanced breast cancer were treated with the regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Their response to the combination chemotherapy and their survival were correlated in respect to estrogen-receptor (ER) status. No patient had rece ived any form of hormonal therapy or other chemotherapeutic agent prior to the CMF treatment. Overall response rate, both complete and partial, to chemotherapy was 60% (21/36): 88% in the ER+ group (14/16) and 35% in the ER- group (7/20). Median duration of response was 17 mo in ER+ and 7 mo in the ER-. Median duration of survival was 27 mo in ER+ patients and 9 mo in ER- patients after initiation chemotherapy. These data suggest ER+ status has a beneficial effect in the responsiveness of advanced breast cancer to CMF chemotherapy and is prognostic of better survival. (Author abstract) (17 Refs)

18. HORMONAL AND CYTOTOXIC CHEMOTHERAPY FOR ENDOMETRIAL CARCINOMA. STEROID RECEPTORS IN THE SELECTION OF APPROPRIATE THERAPY.

Kauppila A, Friberg LG
Dept. Obstetrics and Gynecology, Univ. Oulu, SU -90220 Oulu 22, Finland
Acta Obstet Gynecol Scand [Suppl]; (101):59-64 1981

Progestin therapy yields an objective remission in about one-third of patients with advanced endometrial carcinoma. Cytotoxic chemotherapy has also clearly proved effective in recent yr, and anti-estrogen therapy to an indicative degree. It is remarkable that both these therapies appear to exert their antineoplastic effect even in patients unresponsive to progestin. A survey of current knowledge on estrogen (ER) and progestin receptors (PR) demonstrates that they are present simultaneously in 41-80% of samples of endometrial carcinoma tissue. The concentration of cytosol ER and PR tends to decrease from well differentiated towards anaplastic carcinomas. This indirect evidence, together with some preliminary clinical observations, suggests that an absence or low concentration of ER and/or PR is suggestive of a poor prognosis. It is thought that an assay of ER and PR might be of value in predicting the response to chemotherapy in endometrial carcinoma, such as in breast carcinoma. This does indeed seem to be the case, as at least four independent clinical studies have to date confirmed that significant amounts of cytosol ER alone, and especially cytosol PR alone, or both together, in the tumor tissue can predict with reasonable accuracy a good sensitivity to progestin. In like manner, a low cytosol concentration of these steroid receptors appears to predict a good response to cytotoxic chemotherapy, as demonstrated in one study. Progestin and

anti-estrogen exert their anti-neoplastic effect via an operative receptor mechanism in different ways, whereas cytotoxic chemotherapy acts by means not involving steroid receptors. It is therefore likely that a detailed characterization of the endocrine relations of the tumor by precise assay of ER and PR from the cytosol and nuclear fractions, together with determination of the end-product of progestin action, 17beta-hydroxysteroid dehydrogenase, will further enhance the accuracy of indivi dual a priori selection of the most efficacious chemotherapy available. (Author abstract) (55 Refs)

19. HORMONE RECEPTORS IN RENAL CELL CARCINOMA. THEIR UTILITY AS PREDICTORS OF RESPONSE TO ENDOCRINE THERAPY.

Pearson J, Friedman MA, Hoffman PG
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Cancer Chemother Pharmacol; 6(2):151-154 1981

Estrogen (ER) and progesterone (PR) receptors were studied in 26 patients (22 men, 4 women; 36-84 yr old) with renal cell adenocarcinoma and results correlated with the responses of patients having measurable disease to hormonal therapy. Of the 26 patients, 25 had radical and 1 partial nephrectomy. Only 1/23 tumors assayed for ER had a significant receptor level (186 +-36 femtomole (fmol)/g tissue). Three of 24 tumors assayed for PR had significant titers (564 +-87, 484 +-87, 321 +-138 fmol/g tissue). In 11 tumors assayed, an av 32.4 +-13.3 mg cytosol protein/mg wet tumor tissue was found. Thus the ER+ tumor had a titer of approx 6 fmol/mg cytosol protein, while the highest PR titer was approx 17 fmol/mg cytosol protein. Only one patient had unsuccessful hormonal therapy prior to tissue sampling for ER and PR; the prior therapy could have diminished receptor titers. Ten patients who developed measurable metastatic disease subsequently were treated with hormonal therapy. In all but one, treatment consisted of high-dose progestational therapy administered either po or im. None showed any evidence of tumor regression during or after therapy. The data suggested that few, if any, renal cancers have high titers of ER or PR; those patients whose tumors have low receptor titers are unlikely to respond to hormonal therapy. (17 Refs)

20. CEREBROSPINAL FLUID HUMAN CHORIONIC GONADOTROPIN LEVELS IN NORMAL PREGNANCY AND CHORIOCARCINOMA.

Berkowitz RS, Osathanondh R, Goldstein DP, Martin PM, Mallampati SR, Datta S
New England Trophoblastic Disease Center, Div. Gynecologic Oncology, Brigham and Women's Hosp., Boston, MA
Surg Gynecol Obstet; 153(5):687-689 1981

We measured human chorionic gonadotropin levels simultaneously in the serum and cerebrospinal fluid of 36 normal pregnant women and of 6 patients with choriocarcinoma. During normal pregnancy, human chorionic gonadotropin levels in the cerebral spinal fluid correlated well with those in the serum in both the first and third trimesters. A serum-cerebral spinal fluid human chorionic gonadotropin ratio of less than 60 has previously been reported as a sensitive diagnostic test for trophoblastic CNS involvement. However, we found this ratio to be less than 60 in one patient undergoing first trimester abortion and in one patient with nonmetastatic choriocarcinoma. Furthermore, two patients with documented trophoblastic cerebral metastases had serum-cerebral spinal fluid human chorionic gonadotropin ratios in excess of 60. Results of our study, thus, indicate that determination of a single serum-cerebral spinal fluid human chorionic gonadotropin ratio may not conclusively prove or exclude trophoblastic CNS metastases. Unless it is corroborated by other diagnostic means, a single decreased serum-cerebral spinal fluid human chorionic gonadotropin ratio is insufficient evidence to initiate multimodality treatment for presumptive CNS involvement. (Author abstract) (3 Refs)

21. HCG AND HCG SUBUNITS AS TUMOUR MARKERS IN PATIENTS WITH ENDOCRINE PANCREATIC TUMOURS AND CARCINOIDS.

Oberg K, Wide L
Dept. Internal Medicine, Univ. Hosp., Uppsala, Sweden
Acta Endocrinol (Copenh); 98(2):256-260 1981

Serum levels of hCG, hCG-alpha- and hCG-beta-subunits were measured in 29 patients with APUD-tumors, 16 patients with endocrine pancreatic tumors (EPT) and 13 patients with carcinoids. Twenty out of 29 patients (69%) had elevated level of hCG and its subunits. Among patients with EPT, 11 out of 16 (69%) had raised levels of these peptides. Three patients with benign tumors had normal concentrations, thus giving a frequency of 85% in the group of malignant EPT. In patients with carcinoids 9 out of 13 (69%) had elevated serum levels of at least one of the components. A discordance in secretion pattern between the two types of APUD-tumors was noticed. Only one patient, a case with a carcinoid had raised levels of the complete hCG molecule. The levels of hCG-alpha were elevated in 23% of the patients with malignant EPT and 69% of the patients with carcinoids while the corresponding frequencies of raised hCG-beta levels were 69% and 8%, respectively. Three out of four patients with so-called non-functioning islet cell tumors had raised levels of the subunits. These results indicate that hCG subunits are valuable tumor markers in both of these APUD-tumors, and that malignant EPT predominantly secrete hCG-beta- and carcinoids hCG-alpha-subunits. (Author abstract) (10 Refs)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

22. BIOCHEMICAL CHARACTERIZATION AND CLINICAL EVALUATION OF A HUMAN PANCREAS-SPECIFIC ANTIGEN (MEETING ABSTRACT).

Loor R, Kuriyama M, Shimano T, Manzo ML, Inaji H, Douglass HO, Berjian R, Nicolai JJ, Tytgat GN, Chu TM
Roswell Park Memorial Institute, Buffalo, NY
Newsletter Natl Pancreas Cancer Project; VI(2):36 1981

A pancreas-specific antigen (PaA) has been identified by immunologic techniques and purified from saline extract of human pancreas. The purified PaA has a mol wt of 44,000 and a sedimentation coefficient of 3.4S. PaA possessed an isoelectric point of 4.9 and migrated to alpha-beta region upon immunoelectrophoresis. Immunochemical staining revealed that PaA was located in acinar cells of human pancreas. In addition a higher concentration of PaA was detected in pancreatic juice than in the saline extract of pancreas. A sensitive and reproducible sandwich-type enzyme immunosorbent assay has been developed for quantitation of PaA. With this method, PaA at a concentration as low as 0.8 ng/ml can be detected. Serum PaA levels from 51 healthy persons ranged from less than 4 to 34 ng/ml. Using 21.5 ng/ml (the upper 97.5 percentile of normal

controls) as an upper limit, 50 of 76 pancreatic cancer (66%), 4 of 16 pancreatitis (25%) and 3 of 8 cholelithiasis (38%) had an elevated PaA. Among 16 pancreatitis patients, 3 of 6 (50%) acute pancreatitis and 1 of 10 (10%) chronic pancreatitis patients had an elevated PaA level. In 76 pancreatic cancers, 6 of 10 (60%) stage I, 11 of 18 (61%) stage II, and 33 of 48 (69%) stage III pancreatic cancer patients showed an elevated PaA level. Very few patients with other cancers, however, were shown to have an elevated PaA; 4/56 (7%) of lung cancer, 2/50 (4%) of colorectal cancer, 4/49 (8%) of prostate cancer and 1/39 (3%) of breast cancer. The sensitivity and specificity of serum PaA test for the detection of pancreatic cancer were calculated to be 66% and 95%, respectively. PaA was detected in pancreatic carcinoma by immunocytochemical technique. These results indicate that PaA may be useful as an adjunctive tool in immunodiagnosis of pancreatic cancer. (no Refs)

23. IMMUNOCHEMICAL AND IMMUNOCYTOCHEMICAL LOCALIZATION OF S-100 ANTIGEN IN NORMAL HUMAN SKIN.

Cocchia D, Michetti F, Donato R
Dept. Anatomy, Universita Cattolica, Roma 00168, Italy
Nature; 293(5836):85-87 1981

The presence of S-100 antigen in normal human skin is reported. Levels of S-100 were measured by microcomplement fixation assay in normal skin and in human melanomas using a specific antibody raised against ox S-100. The amounts of S-100 were measured in samples containing 15 or 25 ug total protein; no appreciable anticomplementary activity was observed. The S-100 antigen was detected in measurable amounts in both the normal skin (0.03 ug/mg soluble protein) and melanoma (1.90 ug/mg soluble protein). In normal epidermis, S-100 reaction product was detected by electron microscopy (using the unlabelled antibody Papanicolaous's test with the same antiserum) in the perikarya and in the cytoplasmic processes of both melanocytes and Langerhans cells. No reaction production was present in the keratinocytes of any epidermal layer. In normal dermis, S-100 reaction product was detected not only in typical Langerhans cells, but also in cells with ultrastructural features comparable with Langerhans cells but lacking the characteristic granules. The results indicate that definite cutaneous cell types normally contain significant amounts of S-100 antigen, but at a much lower concentration than in malignant tissue. (22 Refs)

24. ANTIBODIES IN HUMAN SERA REACTIVE AGAINST AN INTERNAL STRUCTURAL PROTEIN OF HUMA N T-CELL LYMPHOMA VIRUS.

Kalyanaraman VS, Sarngadharan MG, Bunn PA, Minna JD, Gallo RC (c/o Gallo) Lab. Tumor Cell Biology, NCI, Bethesda, MD, 20205
Nature; 294(5838):271-273 1981

A limited survey was designed to determine whether natural antibodies reactive against the human retrovirus isolate, HTLV, can be detected in human sera. The assay involved use of a radioimmune precipitation of 125I-labeled HTLV-cr p24 by human sera using a double antibody system. The p24 of HTLV-cr was purified to homogeneity from density-banded virus and radiolabeled with 125I. Serum from patient CR (the source of the isolate) and serum from another patient, MJ, with Sezary syndrome showed high reactivity to HTLV-cr p24. Twenty-one sera from various T-cell malignancies and 50 sera from random normal donors showed no significant precipitating activity. Eleven sera from close family members of patients with T-cell malignancies and previous evidence of HTLV infection were studied. Only one, from the wife of patient CR, reacted strongly in the immunoprecipitation. The antibodies against p24 are present in human sera, and these are specifically directed at HTLV-cr proteins and not at cell-specific determinants. Thus, the immunological reactions are not those reported in human sera against animal virus glycoproteins which, lacking virus specificity, are directed against the carbohydrate residues of the glycoprotein. The antibodies against HTLV are thus the first evidence for a specific immune response in humans against a retrovirus. (15 Refs)

25. COMPARISON OF HISTOLOGIC AND IMMUNOLOGIC HETEROGENEITY OF NON-HODGKIN'S LYMPHOMAS.

Borowitz MJ, Croker BP, Metzgar RS
Dept. Pathology, Duke Univ. Medical Center, Box 3712, Durham, NC, 27710
Am J Pathol; 105(2):97-106 1981

The lymphocyte surface marker phenotype in 11 selected cases of non-Hodgkin's lymphomas was determined with anti-Ig and mouse monoclonal antibodies against human lymphocyte antigens. A complement-mediated cell cytotoxicity assay on suspensions of the tumor cells was compared with an indirect immunoperoxidase technique on frozen tissue sections. Both methods gave good results in tumors with a uniform cell population, but the frozen section technique was superior in heterogeneous tumors. The six B-cell neoplasms were heterogeneous with respect to expression of surface Ig and Ia antigens. The five T-cell tumors were morphologically heterogeneous and also highly variable in their expression of different T-cell specific antigens. (Author abstract) (33 Refs)

26. MALIGNANT LYMPHOMA WITH DUAL B AND T CELL MARKERS. ANALYSIS OF THE NEOPLASTIC CELLS WITH MONOCLONAL ANTIBODIES DIRECTED AGAINST T CELL SUBSETS.

Aisenberg AC, Bloch KJ, Wilkes BM
Huntington Memorial Lab., Massachusetts General Hosp., Boston, MA, 02114
J Exp Med; 154(5):1709-1714 1981

A human malignant lymphoma with characteristics of both B and T cells is reported. Neoplastic lymphocytes from five patients were analyzed. B cell characteristics were indicated by demonstration of surface-bound immunoglobulin containing IgM heavy chains and kappa light chains, an Ia-like antigen, and complement receptors. T cell characteristics were indicated by reaction with monoclonal antibodies for detection of sheep RBC OKT11 receptors (all cases), normal peripheral blood T cell OKT 3 determinant (4 cases), and inducer/helper (OKT4) or cytotoxic/suppressor (OKT8) determinants (4 cases). Cells from two cases formed sheep RBC rosettes. The malignant cells all originated from B lymphocytes of the follicular center. The mechanism of development of cells with dual characteristics is uncertain, but may involve derepression of genetic material, transformation of a stem cell before divergence of B and T lymphocyte differentiation, or neoplastic expansion of a normal cell population that has dual markers. (25 Refs)

27. SURFACE MARKER IDENTIFICATION OF SMALL CLEAVED FOLLICULAR CENTER CELL LYMPHOMAS WITH A HIGHLY FAVORABLE PROGNOSIS.

Rudders RA, Ahl ET, Delellis RA, Bernstein S, Begg CB
New England Medical Center Hosp., 171 Harrison Ave., Boston, MA, 02111
Cancer Res; 42(1):349-353 1982

Between 1976 and 1980, 143 cases of non-Hodgkin's lymphoma have been prospectively analyzed for correlations between surface marker phenotype, histomorphology, and prognosis. This study analyzed 44 adults with tumors classified by Lukes-Collins criteria as small cleaved follicular center cell lymphomas. Two surface marker phenotypic subsets were studied based on the expression of either the second surface membrane Ig, IgD, or a receptor for the third component of the complement system (C'3) (Group I = IgD+ and/or C'3+, Group II = IgD-C'3-). Eleven of the 44 patients have died with a projected median survival of 58 mo. Four patients in Group I have died with a median survival of 58 mo while seven patients in Group II have died with a median survival of 30 mo. The difference in the survival curves for the two subgroups is statistically significant ($p = 0.01$). An analysis of variables such as stage, age, sex, and sites of involvement revealed no differences between the two groups. When classified histologically, the two groups were morphologically indistinguishable and had similar distributions of nodular (follicular) and diffuse variants. Of interest, five patients in Group I were judged to require no initial therapy whereas none in Group II remained untreated initially. The expression of the second heavy chain delta and/or a receptor for C'3 appears to define a subgroup of small cleaved follicular center cell lymphomas with an indolent course and an excellent prognosis. (Author abstract) (20 Refs)

28. PHENOTYPIC HETEROGENEITY AND CELLULAR ORIGINS OF T CELL MALIGNANCIES.

Greaves MF, Rao J, Hariri G, Verbi W, Catovsky D, Kung P, Goldstein G
Membrane Immunology Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Leuk Res; 5(4/5):281-299 1981

The reactivity of the OKT series of monoclonal antibodies was compared with a panel of other monoclonal antibodies, sheep erythrocyte rosette formation, and expression of terminal deoxynucleotidyl transferase in untreated T cell malignancies. Also included in the series were OKT11 and OKT11A, two new monoclonal antibodies with pan-T activity. The composite phenotypes of cells from individual patients were classified according to a presumptive sequence of T lymphocyte differentiation. Six categories of T cell phenotypes were designated, four of thymic type and two of mature T cells. Cells from 82 untreated patients with T cell malignancy were tested with the OKT series of monoclonals and other markers. The OKT defined phenotype of 13 established T cell lines is presented. The most striking result from this analysis was the association between overall phenotype and diagnostic subgroup of T cell malignancy. The results indicated that T cell leukemias have exclusive, composite phenotypes which are in themselves remarkably heterogeneous. It was suggested that T-cell acute lymphoblastic leukemia and T-cell non-Hodgkin's lymphoma in young patients originate in a thymic stem cell with varying levels of maturation arrest, whereas those T malignancies in adults with a mature T cell phenotype arise from long-lived immunocompetent T cells. (79 Refs)

29. INDICATION OF B-LYMPHOCYTIC LEUKEMIA BY MONOCLONAL ANTIBODY ANTI-Y 29/55.

Obrecht JP, Gudat F, Forster HK, Albrecht R, Girard MF, Ludwig C, Christen C
Onkologie, Kantonsspital, Petersgraben, 4, CH-4031 B[illegible], Switzerland
Schweiz Med Wochenschr; 111(41):1529-1531 1981

The monoclonal antibody anti-Y 29/55 recognizes a group specific antigen on sessile human B-lymphocytes which do not belong to the recirculating lymphocyte pool. The occurrence of this antigen in malignant NHL, with or without leukemic state, and in other leukemias has been studied. The antigen was expressed on cells of various histologic B-cell types but not on leukemic cells of ALL, T-lymphoma, AML or CML. It is concluded that in malignant B-lymphoma, B-CLL and HCL, cells appearing in blood carry a marker characteristic of virgin or activated sessile B-lymphocytes. Anti-Y 29/55 permits differentiation of such cells from normal recirculating B-cells and other leukemic cells including ALL, AML and CML. In follow-up studies this antibody may be helpful in detecting early leukemia output. B-lymphocytic leukemia may reflect a disproportion between binding sites on the lymphatic reticulum and the neoplastic cells bearing this a ntigen, which might be involved in binding of B-lymphocytes to the supporting lymphatic reticulum. (Author abstract) (3 Refs) (In GER)

30. IMMUNOLOGICAL STUDIES IN CHRONIC LYMPHOCYTIC LEUKEMIA. I. ELUCIDATION OF SUBSET HETEROGENEITY.

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Leuk Res; 5(4/5):341-348 1981

The B lymphocyte subsets in chronic lymphocytic leukemia (CLL) were examined by three different approaches: rosette sedimentations, double marker assays, and separation of CLL cells according to their densities in continuous Percoll gradients. A hypothesis of sequential alterations of the surface receptor in CLL is presented. RBC and mouse rosette tests yielded complementary results when 30 untreated CLL patients (43-81 yr old) were compared with 10 normal donors. The most stable marker of the malignant B cells was their ability to form rosettes with mouse RBC, while surface membrane immunoglobulins, IgG constant fragment-, and complement receptors were present only on a minor proportion of CLL cells. Lymphocytes forming rosettes with S-aminoethyl-iso-thiouronium bromide-treated sheep RBC were separated from non-rosette forming cells in eight patients; a very high percent of T cells were active RBC-rosette formers. When cells harvested from the non-T fractions were tested for mouse rosette formation, it was found that mouse rosette separation procedures are not as effective as those using sheep RBC: 22% of the cells harvested from the second interface were still able to form mouse rosettes. Double markers were found in 5/5 untreated patients. The surface marker phenotype of large cells, which are frequently seen in CLL patients, was determined. The results indicated considerable heterogeneity in CLL lymphocyte subsets. (25 Refs)

31. USE OF IMMUNOLOGICAL METHODS IN CHARACTERIZING ACUTE LYMPHOBLASTIC LEUKEMIAS IN CHILDHOOD.

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II. Detska klinika, Detska fakultna nemocnica, Duklianska 14, 881 25 Bratislava, Czechoslovakia
Bratisl Lek Listy; 76(2):183-191 1981

Spontaneous and immune rosette tests were performed in 47 children (3-14 yr old) with acute lymphoblastic leukemia (ALL). The tests were performed at the time of diagnosis in 26 cases, and during complete remission in the course of cytostatic therapy in 21. Immunological classification of ALL was possible in 16 cases: null cell type was found in 10 cases, B cell type in 2, T cell type in 1, and T + B cell type in 3. During the 4-30-mo follow-up period there were no differences in the course of the disease between the individual immunological types. Repeated rosette tests showed normalization of the T and B lymphocyte counts shortly after remission had been achieved. In the further course, the T cell count tended to decrease, reaching normal levels only after completion of the cytostatic therapy, while the B cell count remained within the normal range. (20 Refs) (In SLO)

32. UNUSUAL T-CELL PHENOTYPE IN ADVANCED B-CHRONIC LYMPHOCYTIC LEUKAEMIA.

Matutes E, Wechsler A, Gomez R, Cherchi M, Catovsky D
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Br J Haematol; 49(4):635-642 1981

T-lymphocytes isolated by E-rosetting from 22 patients with B-cell chronic lymphocytic leukemia (B-CLL) showed membrane phenotype features distinct from those of normal T-lymphocytes. These changes were particularly marked in advanced disease (Rai Stages II, III, IV and WBC over 100 x 10(9)/l). The most significant finding was the demonstration, in 10 cases, of a major population of E-rosette positive cells (40-80%) unreactive with the OKT monoclonal antibodies against mature or immature T-cells; 15-30% of the cells were unreactive in 7 other cases. A significant reduction in OKT4 positive (helper) lymphocytes was seen in 18 cases. The proportion of OKT8 positive cells was increased in two and normal or low in the rest. Only four patients with early disease (Stages 0 and I) had a normal T-cell phenotype. These findings could explain abnormalities previously described in the T-lymphocytes of B-CLL and provide new insights into the pathogenesis of the disease. (Author abstract) (19 Refs)

33. ANTIGENS EXPRESSED ON HUMAN MYELOID AND T-CELL LEUKAEMIA AND GRANULOCYTE MACROPHAGE-COLONY FORMING UNITS (GM-CFUC) (MEETING ABSTRACT).

Pilkington GR, Januszewicz E, Bradley TR, Jose DG
Immunogenetics Research Unit, Cancer Institute, 481 Lt. Lonsdale Street, Melbourne 3000, Australia
Exp Hematol; 9(Suppl9):50 1981

Antisera have been raised in rabbits to a human acute myelomonocytic leukemia derived cell line (RC2a) and a macrophage like histiocytic lymphoma cell line (U937). These antisera were rendered specific by absorption with pooled B-lymphoblastoid cell lines including the autologous (to RC2a) B-lymphoblastoid cell line CESS-B. Specificity of these sera was tested in a complement dependent microcytotoxicity test against separated normal WBC populations, leukemic cells from over 100 patients and 24 cell lines. Parallel studies of E-rosette receptor, SIg, non-specific esterase and myeloperoxidase expression were performed on these populations. The antisera reacted with myeloid leukemia cell populations from acute myelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia patients and with lymphoid leukemia cells from Null (preT)-acute lymphocytic leukemia (ALL) and T-ALL patients. In addition one of the antisera reacted with approx 70% of mononuclear cells from normal human marrow. This antiserum completely inhibited GM-CFUc formation in agar. The data suggest that these antisera recognize antigens expre ssed on immature cells of myeloid and T-lymphocyte lineage including GM-CFUc. (no Refs)

34. SURFACE MEMBRANE CHARACTERISTICS AND CYTOCHEMISTRY OF THE ABNORMAL CELLS IN NONLYMPHOCYTIC LEUKEMIA.

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Nippon Naika Gakkai Zasshi; 70(4):553-564 1981

The surface membrane characteristics and cytochemistry of the leukemia cells were determined in 20 patients with acute myelogenous leukemia (AML), 2 with acute premyelogenous leukemia (APL), 3 with chronic myelogenous leukemia with malignant change (CMLC), 2 with acute monocytic leukemia (AMoL), 12 with acute-subacute myelogenous monocytic leukemia (MMoL) and with chronic myelogenous monocytic leukemia (CMMoL). The cells were examined for Fcgamma, Fcmu, C3b and C3d receptors by the percentage of rosette-forming cells by means of a microtest plate. Human group AB serum and AKR mouse serum were used as complement. Phagocytosis of the leukemia cells was also determined. Since most of the patients having cytoplasmic granules and peroxidase (PO) among the patients with AML and APL had Fcgamma or C3 receptors, the receptors, granules and PO were considered to appear simultaneously. CML (with malignant change) patients had receptors although only a small amount of enzymes was expressed. All of the patients with AMoL and MMoL had several receptors, and phagocytosis was also detected in all of the patients. Cytochemically, 5 of the 18 patients with AMoL, MMoL or CMMoL completely lacked alpha-naphthyl butyrate esterase in their monocytic leukemia cells, and 7 of the patients partially lacked this enzyme. Phagocytosis was detected in all of the patients, even those who lacked this enzyme. Therefore, the finding of immunological phagocytosis was considered valuable as evidence that a monocytic element constituted the leukemia cell. (20 Refs) (In JPN)

35. DIFFERENTIATION ABILITY OF THE CLL LYMPHOCYTE: AN IMMATURE LYMPHOCYTE OR AN ABNORMAL LEUKEMIC CELL?

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Blood Cells; 7(2):321-339 1981

Patterns of cell differentiation in chronic lymphocytic leukemia (CLL) are discussed. While most cases of CLL correspond to B-cell disease, a few cases are clearly defined as T-cell proliferations and increasing numbers of null cases have been published. Distinctive features of B-cell CLL lymphocytes include: very low levels of monoclonal surface immunoglobulin; presence of receptors for mouse RBC; and presence of dual B and

T markers in a high percentage of cases. The relatively rare T-cell CLL is defined by a characteristic clinical and hematological picture including presence of receptors for sheep RBC, reactivity with anti-T sera, and negative or very low values of terminal transferase. There is less agreement in findings on the very rare null-cell CLL; more sensitive methods of study may be needed to establish it as an entity. While great progress has been made in the understanding of CLL, two questions remain unresolved: (1) Does the proliferating clone correspond to an immature B-lymphocyte, or does it merely represent an abnormal leukemic cell? (2) What is the role of T cells in B-cell CLL? (40 Refs)

36. IMMUNOLOGIC, CLINICOPATHOLOGIC AND PROGNOSTIC FEATURES OF LYMPHOMA OF THE GASTROINTESTINAL TRACT.

Minato K, Shimoyama M, Saito H, Watanabe S
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Jpn J Clin Oncol; 11(2):353-362 1981

Surface marker characteristics of lymphoma cells from 32 patients with histopathologically proven malignant lymphomas with gastrointestinal tract (GI) involvement were investigated. Of 12 patients with primary lymphoma of the GI tract, 6 patients presented with masses in the stomach, 1 patient with a mass of the duodenum, 3 with masses in the ileocecal region, and 2 with multiple tumors of the GI tract. In only 1/12 cases were tumor cells found to have no surface Ig (SIg), and to have E-rosette-forming capacity (ERFC) and human T-lymphocyte antigen (HTLA). Of the 11 other non-T lymphomas, 7 were positive for SIg, 2 were negative, and 2 were undetermined. In the seven B-cell lymphomas, SIg were mu heavy chain in four and gamma chain in three. All non-T lymphoma cells had Ia-like antigen. Of the 20 patients with secondary lymphoma of the GI tract, 6 patients had masses only in the stomach, 1 had masses in the small intestine, and two only in the ileocecal region. In 3/20 cases, tumor cells had no SIg, but had ERFC and/or HTLA. No T-cell markers were found in the other 17 cases. Of these, SIg were detected in eight cases bu not in five cases. All the cases examined, including T-cell type cases, showed Ia-like antigen. (22 Refs)

37. CONTRIBUTION OF IMMUNOLOGIC SURFACE MARKERS TO THE DIFFERENTIAL ANATOMO-PATHOLOGICAL DIAGNOSIS OF MALIGNANT LYMPHOMAS.

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Ann Pathol; 1(3):233-238 1981

The application of immunologic surface marker technics to lymph node cellular suspensions has dramatically modified our understanding of non-Hodgkin malignant lymphomas and has fostered new histologic classifications whose use is gradually becoming wide-spread. In light of this, it is pertinent to ask to what extent conventional immunocytologic technics (spontaneous sheep RBC rosette formation, surface complement-receptor and Ig detection) contribute to pathologic diagnosis. Sixteen tumors or nodes co nsidered after initial evaluation to be possible involved with malignant lymphoma were studied. The diagnoses included eight non-Hodgkin malignant lymphomas (7B, 1T), one Hodgkin's disease, five reactive nodes, one leukemoid reaction and one undifferentiated carcinoma metastasis. The contribution of immunocytochemical technics to diagnosis may be summarized thusly: they allow, in the rare, doubtful case, confirmation of the lymphocytic nature on an extranodal tumor. Also, in most cases they can substantiate the malignant nature of a B-lymphocyte proliferation by showing its monoclonality. Finally they contribute to the recognition of T-lymphocyte proliferations: such T-lymphomas are rare and can be difficult to recognize by traditional histologic and cytologic methods alone. The practical aspects of these technics are briefly discussed, with particular emphasis placed on the correlation of morphologic results and those of immunocytologic marker technics. Finally, beyond its diagnostic interest, this immunocytologic approach, which is presently improved by the use of hybridoma monoclonal antibodies, assumes new importance as a perspective from which to review and reconsider as yet poorly understood diseases such as abnormal immune reactions. (Author abstract) (28 Refs) (In FRE)

38. CHARACTERISTICS AND ACTION OF THE CONCANAVALIN A (CON A)-INDUCED SUPPRESSOR CELLS IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES.

Toge T, Yanagawa E, Nakanishi K, Kohno H, Yamada Y, Hattori T
Dept. Surgery, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi, Hiroshima 734, Japan
Gan To Kagaku Ryoho; 8(5):802-808 1981

After treatment with Con A, peripheral blood lymphocytes from both normal donors and cancer patients contained Con A-induced suppressor cells which depress the proliferative response of lymphocytes from normal donors. Con A-induced suppressor cells were present among E-rosette forming cells. The activities of these cells were apparent when added on day 0 of responder cell cultures. In our assay system, allo-antigen-induced proliferation as well as mitogen-induced proliferation was depressed by Con A-activated cells. In esophageal, colorectal and gastric cancer patients, a significant increase in Con A-induced suppressor cell activity as compared with normal donors was observed, whereas in patients with breast cancer, there was no such increase in activity. In patients with advanced gastric cancer, increased suppressor cell activity was also found, and it decreased significantly after resection of the tumors. The suppressor mechanisms may be of major importance in governing the outcome of antitumor responses. (25 Refs) (In JPN)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

39. LACTIC DEHYDROGENASE IN THE MONITORING AND PROGNOSIS OF TESTICULAR CANCER.

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Cancer; 48(10):2274-2278 1981

In a prospective study of 80 patients with germinal testicular cancer, serial determinations of lactic dehydrogenase (LDH), alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) were followed for a mean of 18.1 mo. Serum LDH was found to be elevated more frequently with increasing tumor bulk. LDH was elevated in 78.0% of the patients with Stage III disease but only 26.3% of the Stage II patients and 20.0% of the pre-orchiectomy Stage I patients. In this study, serum HCG and AFP levels were always elevated in the presence of elevated serum LDH levels except in one patient when LDH

was the only elevated marker, in which case it correlated with clinical disease. Correlation of these three serum markers is shown by elevation of LDH in 78.0% of the Stage III patients, AFP in 78.6%, and HCG in 76.2%. In addition, of the 43 patients who had normal LDH levels on initial presentation, their mean survival time (MST) at the end of the study was 15.5 mo while the 26 patients who had elevated LDH levels on initial presentation had an MST of 9.2 mo. Serum LDH, therefore, may be useful in evaluating patient prognosis as well as an adjunct in monitoring the treatment of patients with bulky testicular cancer. The combination of LDH and HCG has been utilized to monitor the treatment of seminoma. (Author abstract) (16 Refs)

40. FALSE-POSITIVE AND FALSE-NEGATIVE ALPHA-FETO PROTEIN AND HUMAN CHORIONIC GONADOTROPIN ASSAYS IN TESTICULAR CANCER: A DOUBLE BLIND STUDY.

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Cancer; 48(10):2279-2281 1981

The rates of false-positive and false-negative serum alpha-feto protein (AFP) and human chorionic gonadotropin (HCG) determinations in 50 patients with testicular cancer utilizing assays from a reference laboratory were studied. Seven (14%) of 50 patients had false-positive and 1 (2%) of 50 had false-negative serum HCG determinations. Although 6 (12%) of 50 of serum AFP determinations showed false-positive results; no false-negative rates were encountered for serum AFP. Utilizing simultaneous measurements of serum HCG and luteinizing hormone (LH) measuring urinary HCG by a highly specific carboxyl-terminal assay, one may rule out false-positive occurrences of serum HCG in patients with testicular cancer. This double-blind study also confirmed the need for correlating the clinical status of the patients with elevated serum AFP or HCG in patients with testicular cancer before embarking on any therapy. (Author abstract) (6 Refs)

41. THE SERUM LEVELS OF HUMAN ALPHA-FETOPROTEIN, AFP, CHORIOGONADOTROPIN, HCG, PLACENTAL LACTOGEN, HPL, AND PREGNANCY-SPECIFIC BETA1-GLYCOPROTEIN, SP1, ARE OF NO CLINICAL SIGNIFICANCE IN COLORECTAL CARCINOMA.

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Eur J Cancer Clin Oncol; 17(9):1047-1052 1981

Four biochemical tumor markers were measured by radioimmunoassays in sera of 233 patients with colorectal carcinoma. Pre-operative serum levels of AFP, hCG, hPL and SP1 were elevated in 1.3, 5.4, 4.8 and 0.7% of the patients respectively. Post-operative serum levels either increased transiently or were elevated permanently. Even when an elevation of one or more of the markers was fairly stable, it rarely provided useful information, since sensitivity of the test, ie ratio of true positives to all patients with recurrence, ranged from 0% for AFP to 15% for hCG. The predictive value of an elevated level of any marker for the diagnosis of recurrence was either misleading or equivocal, which makes each of no value for decision strategy for the individual patient. Therefore, determination in serum of any of these markers in patients with colorectal carcinoma does not seem to provide useful information for pre-operative diagnosis, nor for post-operative monitoring aimed at the detection of operable recurrence. (Author abstract) (33 Refs)

42. GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITY IN HUMAN BREAST CANCER: LACK OF ASSOCIATION WITH OESTROGEN RECEPTOR CONTENT.

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Acta Pathol Microbiol Scand [A]; 89(4):263-270 1981

The correlation between glucose-6-phosphate dehydrogenase activity and different tumor characteristics was investigated in human breast cancer tissue. The enzyme activity was measured by a histochemical method and the estrogen receptor content by a dextran-coated charcoal assay. The proliferative activity of the tumors correlated positively with the glucose-6-phosphate dehydrogenase activity. No correlation was found between enzyme activity and tumor type and menopausal status, age, TNM-class nor estrogen receptor content. Based on this investigation it is concluded that the activity of glucose-6-phosphate dehydrogenase reflects the proliferative status of the tumor but not the hormone dependency of the tumor. (Author abstract) (24 Refs)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

43. PRELIMINARY EVALUATION OF A NEW TUMOR SPECIFIC GLYCOPROTEIN MARKER (MEETING ABSTRACT).

Schiff R, Kenoff M, Schutt E, Heveran J
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Oncodev Biol Med; AbstractsBook,1:60 1981

Recent studies have demonstrated the presence of a tumor specific glycoprotein (TSG) in the sera of cancer patients with a wide variety of tumors. This study uses an radioimmunoassay meth od to determine TSG levels in normal, benign, and cancer patients' serum. Approx 400 patient samples were analyzed. The results between two laboratories were virtually identical. Of 125 apparently healthy individuals assayed, 120 (96%) were negative. The degree of positivity in cancer patients was dependent upon the staging and possibly the drug regimen. The following cancers were identified: Sarcoma, Hodgkins Disease, various carcinomas, lymphoma, and multiple myeloma. Of 21 patients in clinical remission, 17 were negative. A variety of benign samples from one of the laboratories indicated an approx 80% correct identification. These benigns included endometriosis, cystic disease of the breast, benign hypertrophy of the prostate, inflammatory disease of the bowel, and miscellaneous tumors. The TSG did not appear to be related to carcinoembryonic antigen or other markers tested. The preliminary evaluation has indicated the presence of a tumor marker which may be a useful tool for the physician in the diagnosis of cancer. (no Refs)

44. INCIDENCE AND MOLECULAR VARIANTS OF SP-1 IN PATIENTS WITH TESTICULAR GERM CELL TUMOURS (MEETING ABSTRACT).

Lamerz R, Mann K, Eiermann W, Lohrs U, Nathrath W
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Oncodev Biol Med; AbstractsBook,1:56 1981

SP-1 was determined by commercial radioimmunoassay and enzyme immunoassay in sera of 42 patients with seminoma and 151 patients with non-seminomatous germ cell testicular tumors (NSGCT). The incidence rate was compared to that of alpha fetoprotein (AFP) and human chorionic gonadotropin (hCG) measured by radioimmunoassays developed by our laboratory. None of seminoma patients showed elevated SP-1 levels in contrast to 14/151 (9.3%) patients with NSGCT covering a range of 10 to 896 ng/ml. In comparison to the other 2 established markers, SP-1 elevations were never found in AFP-and hCG-negative nor AFP-positive/hCG-negative cases, but in 2.6% of AFP-negative/hCG-positive and in 6.6% of AFP- and hCG-positive cases. By indirect immunoperoxidase staining technique, SP-1 could be demonstrated in syncytiotrophoblastic giant cells of 11 cases investigated. During follow-up of 9 patients, SP-1 levels were low in comparison to hCG levels, reached their normal range sooner following therapy, and hence were less indicative of tumor disappearance. Gel filtration studies in single cases revealed the existence of a high mol wt variant in addition to the main SP-1 component which coeluted with purified 125-I-SP-1. By the results it is concluded that SP-1 determinations in patients with testicular germ cell tumors give no further significant information to the established tumor markers AFP and hCG. (no Refs)

45. BASEMENT MEMBRANE CHANGES IN BREAST CANCER DETECTED BY IMMUNOHISTOCHEMICAL STAIN ING FOR LAMININ.

Albrechtsen R, Nielsen M, Wewer U, Engvall E, Ruoslahti E
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Cancer Res; 41(12):5076-5081 1981

The distribution of the basement membrane glycoprotein laminin was studied by the immunoperoxidase technique in benign and malignant human breast tissue and in axillary lymph nodes from patients with breast cancer. An antiserum prepared against rat laminin was used. The specificity of this antiserum against laminin was studied using the FL cell line of human epithelial-like cells derived from normal amniotic membrane. The antiserum reacted with these cells in immunoperoxidase staining and precipitated metabolically labeled secreted polypeptides which comigrated with polypeptides with mol wt of 400,000 and 200,000 of rat laminin in sodium dodecyl sulfate:polyacrylamide gel electrophoresis. The neoplastic cells in malignant breast tissues showed strong cytoplasmic staining for laminin, and a positive reaction was also found in lymph node metastases. In some cases in which only micrometastases were present, these cells also stained strongly for laminin. In nonmalignant breast tissues, the epithelial cells of the ducts were positive for laminin, but the staining was weaker than in the carcinomas. Pretreatment of the fixed tissue sections with trypsin markedly enhanced the staining of basement membranes for laminin. In trypsin-treated sections of normal breast tissue and benign lesions, the laminin staining delineated continuous basement membranes. In carcinomas representing the more differentiated types, basement membranes presumably produced by the tumor cells could be revealed by laminin staining, but they were thinner and discontinuous. The poorly differentiated carcinomas lacked organized basement membranes detectable by laminin staining. Our studies suggest that staining for laminin may be a useful adjunct test for detection of micrometastases in lymph nodes. The correlatiop of disintegration of the laminin-containing basement membranes of tumors with increasingly anaplastic appearance supports the notion that basement membranes may play a role in tumor invasion. (Author abstract) (33 Refs)

46. ANTI-HEART FERRITIN ASSAY FOR DIAGNOSIS OF MALIGNANCY (MEETING ABSTRACT).

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Oncodev Biol Med; AbstractsBook,1:58 1981

It is well known that isoferritin pattern in tumor tissue alters to have more acidic components than its normal counterpart. In the ordinally ferritin assay, however, liver or spleen ferritin which is usually located at the most basic end of isoferritin spectrum is generally used as antigen. In the present paper, we will describe an assay of acidic isoferritin (heart ferritin assay) and its implication for the diagnosis of malignancies. Heart ferritin was purified by ultracentrifugation and gel filtration. Anti-heart ferritin sera were raised in rabbit. A 2-site immunoradiometric assay was established using silicon rubber strings as solid phase material. Magnitude of elevation of serum ferritin in patients with malignancies, in particular pancreatic cancer and hepatoma, increased by heart assay as compared to liver ferritin assay. (no Refs)

47. COMPLEX CARBOHYDRATES AS DIFFERENTIATION MARKERS IN MALIGNANT BLOOD CELLS: GLYCOLIPIDS IN THE HUMAN LEUKEMIAS.

Klock JC, Macher BA, Lee WM, Greaves MJ, Lajtha L, Jasmin C, Bessis M, Ross D

1282 Moffitt Hosp., San Francisco, CA, 94143
Blood Cells; 7(2):247-255 1981

Cell surface glycolipids were studied in normal neutrophils and lymphocytes, chronic myelogenous and lymphocytic leukemia cells, and acute myelogenous and lymphoblastic leukemia cells. A few undifferentiated leukemias or leukemias of uncertain lineage were also studied. Glycolipids were extracted with thin layer and gas-liquid chromatography, gas chromatography-mass spectrometry, direct probe mass spectrometry, and enzyme treatment. Twenty glycolipids were identified and sequenced. Human WBC possess glycolipid patterns that distinguish them from other blood cells. Differences in glycolipids occur in WBC of myeloid and lymphoid types. Two main features emerge from study of glycolipids of human leukemic cells: (i) even though cells appear morphologically undifferentiated, all leukemias be classified as myeloid or lymphoid on the basis of their glycolipids; (2) complexity of cell surface glycolipids is positively correlated with their degree of morphological differentiation. No glycolipids were found in leukemic WBC which were not found in normal cells. Glycolipids may be useful as both cell- and differentiation-specific markers in human blood cells. Antigenic differences in human leukemic cells may partly be due to an altered distribution of complex carbohydrates at the cell surface. (11 Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

48. IDENTIFICATION OF ANTIGENIC DETERMINANTS UNIQUE TO THE SURFACES OF CELLS TRANSFORMED BY EPSTEIN-BARR VIRUS.

Kintner C, Sugden B
Div. biology, California Inst. Technology, Pasadena, CA, 91125
Nature; 294(5840):458-460 1981

Four monoclonal antibodies (anti-EBVCS) that detect antigenic determinants unique to the surfaces of Epstein-Barr virus (EBV)-transformed cells but are not associated with virus production were isolated. Cell lines transformed in vitro or those transformed in vivo but not associated with Burkitt's lymphoma bound anti-EBVCS strongly, whereas cell lines from patients with Burkitt's lymphoma bo und them at intermediate levels or not at all. When untreated lymphocytes and lymphocytes exposed to EBV, Concanavalin A, and pokeweed mitogen were assayed, only EBV-exposed lymphocytes expressed EBVCS determinants, which were detectable within 48 hr after infection. Assay of unseparated populations of EBV-exposed primary lymphocytes and immunoglobulin-positive and -negative populations indicated that those cells which express EBVCS determinants are separated as B cells along with those which express the EBV-induced nuclear antigen and that the two antigen-expressing populations are overlapping and may be identical. A polypeptide with an apparent mol wt of 45,000 was precipitated from an EBVCS-positive cell line and was likely to be the molecule which carries EBVCS determinants. The results indicate that EBVCS determinants are expressed at reduced levels on cell lines established from Burkitt's lymphoma patients relative to expression on other EBV-transformed cell lines. EBVCS determinants are among possible determinants recognized by autochthonous, cytotoxic T cells specific for EBV-transformed cells and may therefore be equivalent to lymphocyte determined membrane antigen (LYDMA); this possibility was supported by the finding that EBVCS and LYDMA were expressed with the same time course in lymphocytes infected with EBV in vitro. If the EBVCS determinants are used by cytotoxic T cells to identify their targets, reduced expression of EBVCS on Burkitt's lymphoma cell lines is consistent with these tumor cells having been selected in vivo to survive that cytotoxic response. (18 Refs)

49. MODULATION OF HUMAN T-CELL DIFFERENTIATION MARKERS BY 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

Nagasawa K, Chechik BE, Gelfand EW, Sengupta S, Letarte M, Mak TW
Ontario Cancer Inst., Toronto, Ontario, Canada
Thymus; 3(4/5):307-318 1981

Extent and sequence of changes in level of seven differentiation markers observed in the human leukemia T-cell line MOLT-3 after incubation with 12-O-tetradecanoylphorbol-13-acetate (TPA) were investigated. Terminal deoxynucleotidyl transferase (TdT) activity decreased rapidly after induction with 1.6 x 10(-8) M TPA. The decrease was not simply a loss of enzyme activity, because the percentage of cells containing TdT measured by single-cell immunofluorescence decreased concomitantly. TPA also induced a rapid, irreversible loss of spontaneous proliferative capacity in the cells. Approx 1 day after the addition of TPA, a linear increase in E-rosette-positive (E+) cells was observed. E+ cells increased to approx 50% of the total between days 3 and 4. TPA also caused a gradual decrease in adenosine deaminase (ADA) activity and HThy-L/ADA (human thymus-leukemia-associated antigen, a low mol wt form of ADA) to approx 30-50% of control values. TPA did not induce any significant changes in ecto-5'-nucleotidase activities, in the prolif erative response to phytohemagglutinin, or in the expression of Ia-like antigens. Time kinetics of the changes suggest that the sequence of events induced by TPA is loss of TdT activity, loss of proliferative activity and ability to form E-rosettes, and a decrease in ADA (HThy-L/ADA). This sequence appears to follow that proposed for prethymic precursor T-cell differentiation after activation with thymic epithelium. (35 Refs)

50. INDUCTION OF CYTOTOXIC ACTIVITY IN HUMAN LYMPHOCYTES AGAINST AUTOLOGOUS AND ALLOGENEIC MELANOMA CELLS IN VITRO BY CULTURE WITH INTERLEUKIN 2.

Hersey P, Bindon C, Edwards A, Murray E, Phillips G, McCarthy WH
Medical Res. Dept., Kanematsu Memorial Inst., Sydney Hosp., Sydney, Australia
Int J Cancer; 28(6):695-703 1981

THe influence of interleukin 2 (IL2) on the cytotoxic activity of lymphocytes from patients with melanoma against autologous and a variety of allogeneic melanoma cells was studied. These results suggest that lymphocytes from patients with melanoma are primed against autologous antigens in vivo and that provision of a second signal, IL2, in vitro can induce cytotoxicity against the autologous tumor. The cytotoxicity generated against the allogeneic target cells did not appear to have specificity to melanoma. Several results, such as the pattern of cytotoxicity against the target cells and changes in cell surface markers on the lymphocytes during culture, suggesting that cytotoxicity was mediated by activated T cells rather than by natural killer cells. These findings appear to have important implications both in the understanding of tumor-host relationships and for the use of IL2 in therapy. (39 Refs)

51. COMPARISON OF MONOCYTE AND ALVEOLAR MACROPHAGE ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY AND FC-RECEPTOR ACTIVITY.

Garagiola DM, Huard TK, LoBuglio AF
Simpson Memorial Inst., Univ. Michigan, Ann Arbor, MI, 48109
Cell Immunol; 64(2):359-370 1981

The cytotoxic potential of rabbit peripheral blood monocytes and alveolar macrophages in antibody-dependent cellular cytotoxicity (ADCC) toward both RBC (RBCox) and tumor cell (CEM T-lymphoblast) targets was examined. ADCC was measured in a 4-hr 51Cr-release assay. Alveolar macrophages were more efficient at killing the tumor cell targets (optimally sensitized with rabbit antisera) than monocytes at similar effector cell/target cell (E/T) ratios. Tumor cell targets sensitized with with seven different antisera (anti-CEM) were lysed by alveolar macrophages but not by the monocytes. In marked contrast the monocytes were more effective at lysing the sensitized RBC target cells. The degree of cytolysis of RBCox and CEM was dependent on the E/T ratio and the degree of sensitization of these target cells. It was demonstrated that the effector cell selectivity in ADCC was directly related to their ability or inability to bind the sensitized t arget cells as determined by Fc-receptor rosette formation. The transition from monocyte to macrophage may, therefore, have resulted in an alteration in the criteria necessary for Fc-receptor binding to antibody-sensitized target cells and subsequent ADCC. (Author abstract) (40 Refs)

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. POSTOPERATIVE SCREENING OF PATIENTS WITH CARCINOMA OF THE COLON.

Beart RW, Metzger PP, O'Connell MJ, Schutt AJ
Mayo Clinic, Rochester, MN, 55905
Dis Colon Rectum; 24(8):585-588 1981

A prospective evaluation of 149 patients with Dukes' B2 or C colorectal carcinoma, including periodic history, physical examination, chest radiograph, liver function tests, complete blood count, carcinoembryonic antigen (CEA) radioimmunoassay, barium enema, and endoscopic studies, has been underway since 1976. Thirty-four patients have had recurrence. This study suggests that the history and CEA are the most sensitive noninvasive methods with which to detect recurrent tumors but are unlikely to indicate recurrence at a therapeutically advantageous stage. (Author abstract) (14 Refs)

2. PROGNOSTIC SIGNIFICANCE OF CEA IN COLORECTAL CANCER: A STATISTICAL STUDY.

Persijn JP, Hart AA
Ziekenhuis Amsterdam-Noord, NL-1031 XP Amsterdam, The Netherlands
J Clin Chem Clin Biochem; 19(11):1117-1123 1981

Pretreatment and serial posttreatment levels of carcinoembryonic antigen (CEA) were studied in the sera of 222 patients with colorectal cancer; 205 patients underwent surgery as the primary treatment. Posttreatment levels during the subsequent 6 yr were expressed in actuarial or cumulative plots in relation to tumor-free period, time of diagnosis of recurrence, and time of diagnosis in local and distant recurrences. While pretreatment levels of CEA were significantly elevated, they gave no more prognostic information than that provided by the Dukes classification. Tumor-free periods of Dukes B patients were not significantly different if grouped according to different levels of their pretreatment CEA values. Among 144 patients with pretreatment values greater than 4.9/liter, 20 had residual tumor; two of these patients had CEA values which decreased to less than 5.0/liter within 100 days despite residual tumor, suggesting the possibility of a 'false' decrease. Pretreatment CEA values only had prognostic value in inoperable patients. Elevated pretreatment CEA did not exclude the possibility of curative treatment. Normalization of CEA after surgery did not indicate completeness of cure. In patients with local or distant recurrences, CEA in some instances rose before recurrences became clinically apparent. In approx 40% of patients, clinical diagnosis of recurrence preceded a rise in CEA. Max negative lead time was 385 days. Recurrence without a rise in CEA was exceptional. Results strongly suggest that serial CEA determinations cannot replace physical examination and follow-up. (28 Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

3. CLINICAL SIGNIFICANCE OF IDENTIFICATIONS OF TDT-POSITIVE CELLS BY INDIRECT IMMUNOFLUORESCENCE ASSAY IN BONE MARROW CELLS FROM PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA.

Hida K, Sakamoto S, Kano Y, Tsuboyama A, Suda K, Takaku F
First Dept. Internal Medicine, Jichi Medical Sch., Tochigi, Japan
Nippon Ketsueki Gakkai Zasshi; 44(6):1139-1146 1981

TdT-positive cells in bone marrow mononuclear (bmm) cells from 5 normal adult subjects, 9 patients with CML in chronic phase and 16 patients with CML in blast crisis were examined by indir ect immunofluorescence technique. TdT-positive cells (0.1 to approx 0.6%, mean 0.3%) were found in the bmm cells obtained from five normal adult subjects. No TdT-positive cells were identified in more than one thousand bmm cells from nine patients with CML in chronic phase. On the other hand, 4 to approx 90% of TdT-positive cells were found in the bmm cells from 8 out of 16 patients with CML in blast crisis. Blast cells from eight TdT-negative patients with CML in blast crisis were classified morphologically as myeloid blasts on the basis of Wright-Giemsa stain. Blast cells from six of eight TdT-positive patients were classified morphologically as lymphoid blasts. Blast cells of the other two TdT-positive patients were considered to be a mixture of lymphoid and myeloid blasts morphologically, and in one, the blast cells consisted of both TdT-positive and TdT-negative blast cells. As no TdT-positive cells were found in bone marrow cells from patients with CML in chronic phase, it was considered that assay for TdT-positive cells by immunofluorescence technique might be useful for the earlier detection of TdT-positive blastic transformation of CML. It was also shown that serial observation of bone marrow cells by the indirect immunofluorescence assay for TdT were useful for the assessment of the efficacy of V-P therapy during the course of blast crisis of CML. (22 Refs) (In JPN)

4. DETECTION OF TERMINAL TRANSFERASE IN PARAFFIN SECTIONS WITH THE IMMUNOPEROXIDASE TECHNIQUE.

Halverson CA, Falini B, Taylor CR, Parker JW
Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA
Am J Pathol; 105(3):241-254 1981

Terminal deoxynucleotidyl transferase (TdT) is an early T-cell differentiation marker in a number of species, including man. We have demonstrated TdT in the nuclei of cortical thymocytes in paraffin-embedded sections of calf, rat, and human thymus by indirect immunoperoxidase techniques. In addition, these techniques have been used to verify and extend enzyme assay results by detecting TdT in blast cells from 10 patients with convoluted T-cell lymphoma/leukemia, 1 patient with acute granulocytic leukemia, 1 patient with chronic granulocytic leukemia in blast crisis, and 1 patient with non-T non-B acute lymphocytic leukemia. (Author abstract) (49 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

5. HORMONE RECEPTORS IN BREAST CANCER.

Fortuny IE, Bates HA
(c/o Bates) Res. Lab., Metropolitan Medical Center, 900 South 8th St., Minneapolis, MN, 55404
Minn Med; 64(12):761-763 1981

Standardization, quality control, and results of the hormone receptor assay are discussed. Primary breast cancer specimens were assayed for estrogen (ER), and/or progesterone (PR) hormone receptors. A total of 632/987 (64%) tumors tested were positive. The menopausal state was identified i n 374/632 patients. Histologic description of 229 specimens was: 190 ductal carcinoma, 22 comedocarcinomas, 12 medullary carcinomas, 5 lobular carcinomas, 2 adenocarcinomas. Results obtained disclosed ER positive receptor in 85/145 (58.5%) premenopausal and 147/204 (67.5%) in postmenopausal patients. FR receptors are determined only if ER is positive. For both ER and PR receptors in 180 premenopausal patients were studied showing 133 (73.8%) with both positive receptors. Positive receptors were found in 90/123 (74%) postmenopausal patients. The hormone receptor determinations in breast cancer are important in prognosis and management. Meticulous control of sample storage, handling, periodic double testing of materials, and sample assays are important. (9 Refs)

6. MEASUREMENTS OF DNA SYNTHESIS AND ESTROGEN RECEPTOR IN NEEDLE ASPIRATES AS POWERFUL METHODS IN THE MANAGEMENT OF MAMMARY CARCINOMA.

Nordenskjold B, Skoog L, Wallgren A, Silfversward C, Gustafsson S, Ljung BM, Westerberg H, Gustafsson JA, Wrange O
Karolinska Hosp., Karolinska Inst. and Univ. Linkoping, Linkoping, Sweden
Adv Enzyme Regul; 19:489-496 1981

Techniques used in management of mammary carcinoma (MC) are presented. Monitoring biochemical parameters in small tissue samples from needle aspirates is of value. Measurement of estradiol receptor (ER) in MC is based on the electrofocusing of 3H-estradiol bound receptor in slices of polyacrylamide gel. ER level in the tumor correlates with pathological type of MC. Medullary carcinoma and comedocarcinomas are receptor poor; papillary carcinomas are receptor rich. Measurements of ER and DNA in needle aspirates from primary or recurrent carcinoma correlate significantly. Primary MC from 50 patients were characterized by 3H-thymidine incorporation and ER analysis of needle aspirates. Results correlating with pathological analysis showed that ductal carcinomas of a low degree of differentiation have a decreased mean receptor value. Decreased DNA synthesis can be registered 1-3 wk after initiation of endocrine therapy, before a significant reduction in tumor diameters can be noted. (13 Refs)

7. OVARIAN CARCINOMA: HISTOLOGIC AND CLINICAL CORRELATION OF CYTOPLASMIC ESTROGEN AND PROGESTERONE BINDING.

Creasman WT, Sasso RA, Weed JC, McCarty KS
Div. Oncology, Duke Univ. Medical Center, Durham, NC, 27710
Gynecol Oncol; 12(3):319-327 1981

Primary ovarian carcinomas from 18 patients, ages 27-79, were evaluated for the presence of estrogen- and progesterone-binding proteins. The levels of cytosolic sex steroid receptor were compared to histology, nuclear grade, and the patients' clinical course. The data suggest that nuclear grade and receptor status each correlate with the patients' clinical course. The simultaneous presence of both estrogen and progesterone receptor proteins tend to be noted in tumors with more well-differe ntiated nuclei. It is suggested that the determination of biochemical cytosolic receptor status may become an important addition to tumor type, nuclear grade, and staging as prognostic indicators in patients with ovarian carcinoma. Histochemical staining for estrogen-binding localization did not correlate with SDGA and DCCA receptor analysis nor with clinical parameters. (Author abstract) (31 Refs)

8. CLINICAL COURSE OF CHORIOCARCINOMA AND RESULTS OF TREATMENT OF CHORIOCARCINOMA.

Maruo T, Tojo S, Ashitaka Y, Harada A
Dept. Obstetrics and Gynecology, Kobe Univ. Sch. Medicine, Kobe, Japan
Nippon Gan Chiryo Gakkai Shi; 16(4):704-712 1981

Effects of chemotherapy and surgery were studied in 29 women with choriocarcinoma. Metastatic lesions were observed in 23/29; 22/29 had lung metastases, 10/29 had brain metastases, 5/29 had vaginal metastases, and 4/29 had kidney metastases. One course of combination chemotherapy consisted of methotrexate (15 mg/day x 7 days), actinomycin D (0.5 mg/day x 5 days), adriamycin (10 mg/day x 5 days), and vinblastine (10 mg/day, 1x/wk). Av pretreatment levels of human chorionic gonadotropin (hCG) were 21,300 IU/liter in 6/29 patients who did not have involvement of cancer outside the uterus; all six had complete remission following hysterectomy and an av of 1.5 courses of chemotherapy. Av pretreatment levels of hCG were 70,700 IU/liter in nine patients who had only lung metastases; 7/9 had remission following hysterectomy and an av of 5.5 courses of chemotherapy. Av pretreatment levels of hCG were 211,500 IU/liter in nine patients with metastases to the lung and other organs; 1/9 had remission following surgery and 13 courses of chemotherapy, and 8/9 died within 3 mo of treatment. Av pretreatment levels of hCG were 197 IU/liter in three patients with lung or brain choriocarcinoma and without evidence of uterine lesions; all three had remission, but two had recurrence thereafter. Levels of hCG were thought to have clinical significance as markers of prognosis in patients with choriocarcinoma; follow-up of patients for 2 yr after remission was thought to be important. (12 Refs) (In JPN)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

9. CHRONIC LYMPHATIC LEUKEMIA OF B-CELL TYPE: CLINICAL AND MORPHOLOGICAL INVESTIGATIONS FOR DIAGNOSTIC DIFFERENTIATION.

Schwarzmeier JD, Radaszkiewicz T, Graninger W, Hofer F, Paietta E, Moser C
I. Med. Univ.-Klinik, Lazarettgasse 14, A-1090 Wien, Austria
Klin Wochenschr; 59(23):1313-1318 1981

Chronic lymphatic leukemia (CLL) was diagnosed in 71 patients based on clinical data. Most of the patients were in the stages 0, I and II; only 18% were in the stages III and IV according to Rai. In all cases, the disease was characterized by an increased number of B lymphocytes (B-CLL). The B cells

mostly expressed a weak fluorescence intensity when tested for membrane bound immunoglobulins (Ig). In accordance to that, the quantitative measurement of Ig in the serum revealed a decrease of one or more Ig classes in 72% of the patients. No correlation existed between the number of B lymphocytes (and T lymphocytes) or the Ig concentration in the serum and the stage of the disease. To distinguish the CLL from related lymphoproliferative disorders, especially the immunocytic lymphoma, lymph node biopsies were examined histologically and immunomorphologically for intracytoplasmic Ig. This examination confirmed the diagnosis of CLL in 33 out of 40 cases. Six lymph nodes were classified as immunocytic lymphoma of the lymphoplasmacytoid type. In three of the latter, the immunocytic lymphoma was clinically associated with decreased Ig concentrations in the serum. These findings emphasize that the clinically established diagnosis of CLL should be corroborated by immunomorphology. (Author abstract) (26 Refs) (In GER)

10. ADVANCED CUTANEOUS T CELL LYMPHOMA (TUMEURS D'EMBLEE TYPE): THE DIFFERENTIAL CAPACITY OF E CELL ROSETTING, NON SPECIFIC ESTERASE STAINING AND ANTI-HTLA PEROXIDASE METHODS FOR CYTOLOGICAL DIAGNOSIS (MEETING ABSTRACT).

Holden CA, Staughton RC, MacDonald DM
Department of Dermatology, Guy's Hospital, London, England
Br J Dermatol; 105(3):346 1981

The diagnosis of cutaneous T cell lymphoma depends on cytological typing but T lymphocyte markers are sequentially lost during in vitro transformation. Sections from the cutaneous nodules of a 71-yr-old male with tumeurs d'emblee type cutaneous T cell lymphoma were examined by three commonly used methods for T lymphocyte identification. (1) Collagenase incubated skin was mechanically disintegrated to release viable cells. The proportion of cells retaining the ability to rosette sheep RBC was estimated. (2) Cryostat sections of prefixed frozen tissue were stained for the presence of acid-alpha-naphthyl acetate esterase (ANAE) activity. (3) Tissue sections were incubated with anti-human thymus lymphocytic antigen (HTLA) serum and peroxidase conjugate, and examined by light and electron microscopy to reveal the proportion of cells retaining the HTLA membrane antigen. Six percent of the extracted cells were capable of E rosetting. ANAE activity of T pattern was present in only occasional cells. The immunoperoxidase technique demonstrated characteristic positive labelling of the majority of infiltrating cells. Ultrastructural examination confirmed the presence of HTLA membrane antigen on the cell membrane. The results demonstrate, in vivo, the persistence of HTLA membrane antigen in cutaneous lymphoma T cells which have lost their ability for E rosetting and their ANAE activity. They support the in vitro findings of sequential loss of cell characteristics and suggest that the demonstration of HTLA may identify T lympho cytes which could otherwise be considered as null cells. (no Refs)

11. COEXISTENCE OF A PRIMARY IMMUNODEFICIENCY DISORDER AND HODGKIN'S DISEASE: EVIDENCE AGAINST A B-LYMPHOCYTE ORIGIN FOR THE REED-STERNBERG CELL.

Bobrove AM, Onder O, Myers TJ, Rickles FR, Pastuszak WT, Martin RS, Hild DH
Palo Alto Medical Clinic, 300 Homer Ave., Palo Alto, CA, 94301
Cancer; 48(12):2624-2629 1981

A 44-yr-old woman with a life-long history of recurrent sinopulmonary infections developed Hodgkin's disease with characteristic Reed-Sternberg cells in a biopsy specimen of a mediastinal lymph node. Hypogammaglobulinemia was documented on several serum determinations and plasma cells were absent from biopsy specimens of the lymph node and bone marrow. Immunochemical studies failed to demonstrate any B lymphocytes bearing surface immunoglobulin or Fc-receptors for IgG in the peripheral blood. Pokeweed mitogen stimulation of the patient's peripheral blood lymphocytes in vitro resulted in the development of virtually no plasma cells. Peripheral blood T-lymphocyte number and function were defective initially. Following chemotherapy and radiotherapy, peripheral blood E-rosette-forming cells returned to normal, but T-cell function remained defective and B lymphocytes remained undetectable. These findings are compatible with the presence of two separate immune disorders: a primary hypogammaglobulinemia and Hodgkin's disease. The absence of lymphocytes bearing surface Ig or Fc-receptors for IgG in this patient adds further support against a B-lymphocyte origin for the Reed-Sternberg cell. (Author abstract) (32 Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

12. EVALUATION OF PLEURAL AND ASCITIC FLUID CEA AND HCG LEVELS EXPRESSED AS DIRECT CONCENTRATION AND IN TERMS OF EFFUSION PROTEIN CONCENTRATION FOR DETECTION OF MALIGNANT TUMORS (MEETING ABSTRACT).

Couch WD
Department of Pathology, Baylor University Medical Center, Dallas, TX, 75246
Am J Clin Pathol; 76(3):348 1981

Combining cytology (cytol) with an effusion human chorionic gonadotropin (hCG) and carcinoembryonic antigen (CEA) assay may increase the detection of malignant (mal) tumors associated with pleural (pl) and ascitic (asc) effusions. The following study compares cytol with hCG and CEA assays expressed as concentrations (conc) and effusion total protein conc for tumor detection. CEA (Roche, RIA), hCG (Serono, RIA) and protein (prot) conc (ABA 100) were determined on random pl (n equals 48) and asc (n equals 33) fluids submitted for cytol from 81 patients of whom 55 had mal tumors. Assay levels considered mal were: CEA greater than or equal to 10 ng/ml, hCG greater than or equal to 10 mIU/ml, CEA greater than or equal to 500 ng/g prot, and hCG greater than or equal to 500 mIU/g prot. The following degrees of sensitivity (%) and specificity (%) were obtained for direct conc (ng or mIU/ml): CEA 47 and 88, hCG 36 and 96; CEA and hCG 69 and 88; CEA, hCG and cytol 76 and 88; CEA and cytol 67 and 88; hCG and cytol 55 and 96; cytol alone 40 and 100 and for effusion prot conc (ng or mIU/g prot): CEA 33 and 96, hCG 31 and 96; CEA and hCG 53 and 92, CEA and cytol 64 and 96, hCG and cytol 53 and 96; CEA, hCG and cytol 69 and 92. The results suggest effusion hCG and CEA levels provide a useful adjunct to cytol for the detection of mal tumors. (no Refs)

13. THE SIGNIFICANCE OF TUMOR MARKER ASSAY IN THE STAGING OF BREAST CANCER. ASSESSMENT OF FERRITIN AND BETA-HCG LEVELS.

Micali B, Gioffre Florio MA, Venuti A, Giorgianni G, Saitta FP
Istituto di I Patologia Chirurgica, Policlinico Universitario Gazzi, 98100 Messina, Italy
J Nucl Med Allied Sci; 25(3):65-70 1981

The relationship between the clinical stage of breast cancer and serum levels of ferritin and beta-human chorionic gonadotropin (b-HCG) was studied in 45 post-menopausal patients. Serum ferritin (nanog/ml) levels in patients with regional lymph node involvement were significantly greater than those in the patients without node involvement (102.17 +-27.0 vs 51.53 +-17.2). Ferritin levels showed progressive increase in the patients with metastatic disease, compared with M0 patients. Tumor size was not related to serum ferritin levels. The b-HCG levels was not related to the clinical TNM stage of breast cancer. (14 Refs)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

14. THE CLINICAL LABORATORY DIAGNOSIS OF NEUROBLASTOMA AND PHEOCHROMOCYTOMA.

Kincaid HL
Children's Hosp. Natl. Medical Center, Washington, DC
Clin Proc Child Hosp Natl Med Cent; 37(6):368-376 1981

Clinical application of assay techniques for measuring catecholamines to the detection of neuroblastoma and pheochromocytoma in children is discussed. The higher concentrations of catecholamines in pheochromocytomas indicated that tumor tyrosine hydroxylase is less sensitive to product inhibition than that in the normal tissue. Human neuroblastoma cells were found to contain the enzymes required for catecholamine synthesis, but the relative absence of storage granules was shown to result in rapid degradation of the newly synthesized epinephrine (E) and norepinephrine (NE) to vanilmandelic acid (VMA), as well as in the increase of dopamine (DA) production. The use of high performance liquid chromatography (HPLC) and radioenzymatic assay (REA) provides for an increased detection rate of catecholamines and a variety of metabolic intermediates. HPLC separates E, NE, and DA. The REA approach also offers improved sensitivity and specificity compared with fluorometric assays. (15 Refs)

15. RADIOIMMUNOASSAY OF THYROGLOBULIN IN HUMAN SERUM: CONCENTRATIONS IN NORMAL SUBJECTS AND IN PATIENTS WITH THYROID DISEASE.

Roti E, Robuschi G, Emanuele R, Bandini P, Gnudi A
Cattedra di Endocrinologia e Patologia Costituzionale, Univ. Parma, Via Gramsci 14, 43100 Parma, Italy
J Nucl Med Allied Sci; 25(3):57-63 1981

A specific radioimmunoassay for detection of thyroglobulin (hTG) in the blood sera of the patients with various thyroid diseases was developed. Mean value of hTG in the blood sera of healthy controls was 18.2 nanog(ng)/ml. Higher than normal concentrations of hTG were detected in patients with toxic Grave's disease (213.9 ng/ml), idiopathic hypothyroidism (46.8 ng/ml), euthyroid goiter (164.6 ng/ml), and in th euthyroid and hyperthyroid states of nodular goiter (164.6 and 168.0 ng/ml, respectively). Concentrations of hTG in the patients with thyroid cancer (before thyroidectomy) ranged from 25 to 2,750 ng/ml. Values in these patients were in part comparable to those of other thyroid patients, hence indicating limited value as a marker in diagnosis of thyroid cancer. (17 Refs)

16. SERUM TRANSCOBALAMIN II LEVELS IN BREAST CARCINOMA PATIENTS.

Rachmilewitz B, Sulkes A, Rachmilewitz M, Fuks Z
(c/o Sulkes) Dept. Radiation and Clinical Oncology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 17(9/10):874-878 1981

Serum levels of transcobalamin II (TCII) were determined in 139 patients with breast carcinoma. The patients were divided into two groups. Group A consisted of 74 patients with no evidence of active disease at the primary site or in complete remission. Serum levels of TCII were normal (up to 1,500 pg/ml) in 60 patients (81%) and moderately elevated (up to 1,900 pg/ml) in 14 patients (19%) in this group. Group B consisted of 65 patients with active disease. Serum TCII levels were normal in 23 patients (35%) and were markedly elevated (up to 2,500 pg/ml) in 41 patients (65%). In Group B, 56 patients had widespread metastatic disease and 9 had active locoregional disease. Whether the moderately elevated TCII in the 14 patients of Group A with no evidence of disease and the normal TCII in the 23 patients of Group B with active disease is of prognostic value, will be determined by follow-up and close monitoring of the patients. Preliminary results of serial determinations of TCII indicate that changes in the TCII level generally correlate with the clinical course of the disease and the effects of therapy. These data indicate that TCII serum level may be useful as a marker for tumor activity in breast carcinoma. (Author abstract) (36 Refs)

17. LOSS OF BETA2 MICROGLOBULIN FROM THE SURFACE OF CUTANEOUS MALIGNANT AND PREMALIGNANT LESIONS (MEETING ABSTRACT).

MacKie RM, Turbitt ML
Department of Dermatology, University of Glasgow, Glasgow, Scotland
Br J Dermatol; 105(3):343 1981

At present the cell surface changes associated with the transition from benign to premalignant to malignant counterparts are poorly understood. They are, however, essential to our understanding of events leading to metastatic spread of tumor cells. Beta 2 microglobulin is the light polypeptide chain of the human WBC antigen (HLA) system and is found on the surface of all normal human cells in vivo. We have studied beta 2 microglobulin on the surface cell of twenty-three cutaneous malignancies and twenty-two premalignant or benign skin tumors by the immunoperoxidase immunoenzyme bridge technique. All benign skin tumors (basal cell papillomas, keratoacanthomas) showed beta 2 expression on the cell membranes and all malignant tumors (squamous carcinomas, Bowen's disease and basal cell carcinoma and malignant melanoma) showed an absence of surface beta 2 microglobulin. Actinic keratoses were used as a model of a premalignant condition and in eight out of ten cases some degree of loss of beta 2 microglobulin staining was observed. It would therefore appear that loss of the beta 2 microglobulin cell surface marker correlates well with cell surface changes associated with malignant transformation. (no Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

18. STUDIES OF EXPERIMENTAL OLIGODENDROGLIOMA WITH SPECIAL REFERENCE TO THE ULTRASTRUCTURE AND IMMUNOHISTOCHEMICAL LOCALIZATION OF S-100 PROTEIN, GLIAL FIBRILLARY ACIDIC (GFA) PROTEIN AND GALACTOCEREBROSIDE.

Takahashi K
First Dept. Pathology, Sch. Medicine, Gunma Univ., Maebashi-shi, Gunma Pref. 371, Japan
No To Shinkei; 33(7):703-714 1981

Ethylnitrosourea-induced experimental oligodendrogliomas in rats were investigated by light and electron microscopy and immunohistochemically with antisera to S-100 and GFA proteins and anti-galactocerebroside antibody. Sixty-six neuronal and non-neuronal tumors were produced in 44 litters treated with ethylnitrosourea through the mothers; 43 were in the CNS. Twenty-six of the tumors were oligodendrogliomas, of which 7 showed the histology typical of oligodendroglioma and 19 that of oligodendroglioma mixed with astrocytoma or anaplastic glioma. S-100 and GFA proteins were located immunohistochemically. Astrocytic elements showed positive staining for S-100 and GFA proteins. Anaplastic glia were also weakly positive. No GFA protein was found in oligodendroglioma tumor cells. Some of the oligodendroglioma cell nuclei contained S-100 protein. The cytological distribution of galactocerebroside was determined with immunoperoxidase. Galactocerebroside was detected in interfascicular cells in the white matter as well as in normal ependymal cells and choroid plexus epithelium, but the component cells of oligodendroglioma were negative. Electron microscopy of eight tumors showed loosely arranged small dark cells with very sc anty cytoplasm and a few, delicate, short cytoplasmic processes. Occasional cells contained a microtubular structure about 25 nm in width dispersed in the cytoplasm. The extracellular space was abundant. Astrocytic elements were found in seven of the tumors. The cells had longer and more prominent cell processes containing bundles of glial filaments. The cells in oligodendroglioma appear to preserve the ultrastructural features described by Mori and Leblond for normal oligodendrocytes. (30 Refs) (In JPN)

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. PROGNOSTIC SIGNIFICANCE OF CEA IN BREAST CANCER: A STATISTICAL STUDY.

de Jong-Bakker M, Hart AA, Persijn JP, Cletca FJ
(c/o Persijn) Dept. Clinical Chemistry, Antoni van Leeuwenhoek-Huis/Netherlands Cancer Inst., Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Eur J Cancer Clin Oncol; 17(12):1307-1313 1981

A statistical evaluation was carried out of serial CEA plasma levels in breast cancer patients. The study included 206 patients with operable primary tumor, 108 patients who were inopera ble, 55 patients with advanced disease treated by oophorectomy and 77 post-menopausal patients treated with various endocrine regimens. The pretreatment CEA level was found to have no relation to prognosis. A rise in CEA during the follow-up period was usually associated with progressive disease. In 35% of the cases a rise in CEA preceded clinical signs of recurrence and metastases by an av of 200 days. The practical value of CEA in the management of breast cancer is limited because many tumors do not produce CEA. In CEA-producing tumors it provides a useful aid in clinical evaluation. The need for a strict statistical evaluation of CEA data in the follow-up of breast cancer patients is stressed. (Author abstract) (18 Refs)

2. PROGNOSTIC VALUE OF PREOPERATIVE SERUM CEA LEVEL COMPARED TO CLINICAL STAGING. I. COLORECTAL CARCINOMA.

Staab HJ, Anderer FA, Brummendorf T, Stumpf E, Fischer R
(c/o Anderer), Friedrich-Miescher-Laboratorium der Max-Planck-Gesellschaft, Spemannstrasse 37-39, 7400 Tubingen, W. Germany
Br J Cancer; 44(5):652-662 1981

In a clinical investigation of observed postoperative survival, 563 patients have been registered for primary surgical treatment of colorectal cancer since 1974. The potential prognostic factors examined within the first days of hospitalization for primary resection included age of the patients, operability, location of the tumor, tumor extension and the preoperative serum CEA level. Statistical treatment of the data revealed that each of the clinical parameters except tumor location covers ranges associated with highly significant differences in survival of the patients. The preoperative serum CEA level gave prognostic information in addition to operability of tumor extension. The prognostic significance of the preoperative CEA level was still evident when selected subgroups of patients with distinct resectability and tumor extension were examined. The results indicate that the preoperative serum CEA level is an independent prognostic parameter. (Author abstract) (18 Refs)

3. CARCINOEMBRYONIC ANTIGEN IN CARCINOMA OF THE UTERINE CERVIX: ANTIGEN DISTRIBUTION IN PRIMARY AND METASTATIC TUMORS.

van Nagell JR, Hudson S, Gay EC, Donaldson ES, Hanson M, Powell DF, Goldenberg DM
Gynecologic Oncology, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40506
Cancer; 49(2):379-383 1982

Immunohistochemical staining for carcinoembryonic antigen (CEA) was performed on primary tumors and regional lymph nodes from 100 patients undergoing radical hysterectomies and pelvic lymphadenectomies for invasive carcinoma of the uterine cervix. Antigen staining was present in 82% of keratinizing squamous carcinomas as compared with 50% in nonkeratinizing tumors. Seventeen patients with CEA-producing cervical cancer had regional lymph node metastases, all of which stained positively for CEA. Convers ely, antigen could not be detected in lymph nodal metastases from primary tumors devoid of CEA. The pattern and intensity of CEA staining in primary tumors and their metastases were similar in all cases. Antigen was present in highest concentrations in the cytoplasm and tumor cell membrane of all tissues examined and isolated nuclear staining was absent. The clinical implications of these findings are discussed. (Author abstract) (21 Refs)

4. SIMULTANEOUS ENZYME IMMUNOASSAY OF CARCINOEMBRYONIC ANTIGEN IN PLEURAL EFFUSION AND SERUM.

Asseo PP, Tracopoulos GD
(c/o Tracopoulos) 10th Medical Unit, Athens Chest Hosp. 'Sotiria', Messogeion 152, Athens, Greece
Am J Clin Pathol; 77(1):66-71 1982

A carcinoembryonic antigen (CEA) enzyme immunoassay test was used to estimate its value in the differential diagnosis of malignant and non-malignant pleural effusions. Paired pleural fluid and serum CEA determinations were performed in 107 patients, 53 with malignant and 54 with non-malignant pleural disease. CEA values uniformly lower than a cut-off level of 5.0 ng/ml were found in the pleural fluid and the serum in the non-malignant group, whereas in the malignant group, values higher than the cut-off level were present in the pleural fluid in 37 (69.8%), and in the serum in 30 (56.6%) of the examined patients. All 30 patients with elevated serum CEA levels also had pleural fluid CEA above 5.0 ng/ml. The results of this study demonstrate that although pleural fluid CEA values below 5.0 ng/ml do not exclude malignancy, increased values strongly suggest that the fluid is of malignant origin. Pleural fluid CEA determination had a 13.2% higher sensitivity, compared with that of the serum, in detecting malignant pleural involvement, yet with no statistical significance. (Author abstract) (27 Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

5. SERUM AND BONE MARROW RADIOIMMUNOASSAY OF ACID PHOSPHATASE IN PROSTATIC CANCER.

Sarosdy MF, Kledzik G, Lamm DL
Div. Urology, Univ. Texas Health Science Center, San Antonio, TX, 78284
Urology; 19(1):33-36 1982

Use of radioimmunoassay (RIA) for determinations of prostatic acid phosphatase has recently received considerable attention because of reported higher sensitivity and specificity than previous enzymatic assays. We have compared the sensitivity and specificity of a commercially available RIA to a highly specific enzymatic assay (thymolphthalein monophosphate) using 37 patients with prostatic cancer and 34 patients with surgically proved benign prostatic hyperplasia. Seventeen of the cancer patients and all 34 of the BPH patients were studied prospectively. We further evaluated specificity by performing the RIA on 25 specimens of bone marrow from patients with nonprostatic disease. Our results indicate that radioimmunoas-

say is not, at this time, an adequate screening tool, and we question its accuracy in staging patients any more reliably than by enzymatic assay. (Author abstract) (16 Refs)

6. GLUCOSE-6-PHOSPHATE DEHYDROGENASE: A POSSIBLE CLINICAL INDICATOR FOR PROSTATIC CARCINOMA.

Zampella EJ, Bradley EL, Pretlow TG

(c/o Pretlow) Dept. Pathology, Univ. Alabama Medical Center, University Station, Birmingham, AL, 35294

Cancer; 49(2):384-387 1982

Any system of biochemical analysis that can be used to detect chemical differences between normal and malignant cells may and potentially valuable information to complement the histologic data which provide the practical definition of human prostatic carcinoma. A difference (p less than 0.0001) was observed in the levels of glucose-6-phosphate dehydrogenase (G-6-PD) activity in prostatic tissue with benign hyperplasia and prostatic carcinoma. Measured as a function of the amount of protein extracted from whole-tissue homogenates, the values for G-6-PD activity in prostatic carcinoma are almost 4x those measured for benign prostatic hyperplasia. The degree of elevation of the activity of this enzyme suggests a correlation between enzymatic activity and clinical prognosticators, ie, histologic differentiation and clinical stage. (Author abstract) (15 Refs)

7. II-EVALUATION OF THE PROGNOSTIC VALUE OF THE PLASMA LYSOZYME LEVELS IN LEUKEMIA PATIENT DURING THERAPY.

Talageri VR, Seshadre KN, Advani SH

Cancer Res. Inst., Tata Memorial Hosp., Tata Memorial Center, Parel, Bombay 400 012, India

Indian J Cancer; 18(4):262-267 1981

The prognostic value of plasma lysozyme during management of leukemia patients and the correlation of plasma lysozyme levels with those of leukocytes in these patients were investigated. Plasma was obtained from 53 normal subjects and 14 patients with various types of leukemia. These patients were examined at various stages of their disease. A good correlation between WBC count and plasma lysozyme was observed in 8/14 patients. The case histories of three representative patients in whom such a correlation was observed are reported. Plasma concentrations of lysozyme were found to be high before treatment, fell to normal levels during remission, or levels diminished following partial response to treatment and rise during resistance to treatment. Pre-treatment elevated levels of the enzyme in two patients were associated with high leukocyte counts. With the diminution of WBC count, enzyme levels decreased. In three cases where the WBC counts were initially high, lysozyme levels were either elevated or on the upper limit of normal. Results indicate that plasma lysozyme has limited usefulness as a marker in the management of leukemia. (10 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

8. HORMONE RECEPTORS AND BREAST CANCER.

Howanitz JH

Div. Clinical Pathology, Dept. Pathology, State Univ. of New York, Upstate Medical Center, 750 East Adams St., Syracuse, NY, 13210

Hum Pathol; 12(12):1057-1059 1981

Prognostic value of measurement of cytoplasmic estrogen receptors (ER) in breast cancer patients (BC) is discussed. ER analysis was shown to improve the response rate from 30% in unselected patients to 55% in ER positive BC patients. The presence of ER in a biopsy specimen was found to correlate with the positive response to the decrease of estrogen level, although the ER assay did not always predict the response to endocrine therapy. The discrepancies in the results of ER assay and the response to the endocrine therapy can be explained by improper specimen handling, wrong classification of ER status, or qualitative changes in ER status during tumor progression. Measurements of unoccupied nuclear ER may be useful in identifying the group of BC patients who can benefit from antiestrogens. Measurements of progesterone receptors can be used as an indicator of functioning ER. In addition to steroid hormone receptors, prolactin or growth hormone receptors might be useful in predicting the response to hormone therapy. (5 Refs)

9. HORMONE RECEPTOR ANALYSIS AND TESTING FOR SENSITIVITY TO CYTOSTATIC DRUGS: VALUE IN PLANNING OF ADJUVANT THERAPY FOR MAMMARY CARCINOMA.

Schlag P, Schrenl W, Veser J, Herfarth C

Klinik fur Allgemeine Chirurgie der Universitat, Steinhovelstr. 9, D-7900 Ulm, W. Germany

Dtsch Med Wochenschr; 106(51/52):1749-1754 1981

The significance of tests for hormone receptors and sensitivity to cytostatic drugs (CS) in planning therapy for mammary carcinoma (MC) is reviewed. Assays of tumor tissue extracts (cytosols) by hormone-binding methods such as the charcoal absorption technique allow detection of tumor cell receptors for estradiol (ED), progesterone (PG), androgen, and prolactin, of which the first two have principal clinical significance. ED receptors (EDR) are found in 60-85% of MC; PG receptors (PGR) are found in approx half of MC. Hormonal therapy produces a response of 50-60% in MC with EDR and 83% in MC with both EDR and PGR. EDR and PGR status determinations therefore are important in determining treatment. CS tests include in vivo transplantation in mice and in vitro incubation with cytostatic drugs. A disadvantage of in vitro tests is related to possible cell selection and other factors, not accurately reflecting the actual behavior of the tumor in the patient. In one series of cases only approx 30% of MC could be successfully worked up and evaluated. The value of CS testing, in contrast to the established value of EDR and PGR testing, is uncertain in planning of adjuvant therapy. (52 Refs) (In GER)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

10. HEPATOCELLULAR CARCINOMA ARISING IN NONCIRRHOTIC AND HIGHLY CIRRHOTIC LIVERS: A COMPARATIVE STUDY OF HISTOPATHOLOGY AND FREQUENCY OF HEPATITIS B MARKERS.

Okuda K, Nakashima T, Sakamoto K, Ikari T, Hidaka H, Kubo Y, Sakuma K, Motoike Y, Okuda H, Obata H
Dept. Medicine, Chiba Univ. Hosp., Chiba, Japan
Cancer; 49(3):450-455 1982

Hepatocellular carcinoma (HCC) associated with cirrhosis and HCC developing in a noncirrhotic liver may have differing pathogeneses. To study this possibility, 426 autopsied cases of HCC were investigated. Of these, 45 livers were not cirrhotic, 50 were highly cirrhotic (liver wt less than 99 g), and the remaining 331 were cirrhotic but not so highly. The av age was significantly older in the highly cirrhotic group, suggesting a longer premalignant period of chronic liver disease. The liver wt in the noncirrhotic group was about 3.5 times that in the highly cirrhotic group. Hepatitis B surface antigen was positive in serum in only 9.3% and in liver tissue in 10% in the noncirrhotic cases, the positivity rate being much lower compared with other groups (p less than 0.005-0.01), yet antibody to HB core was positive in 90%. The antibody titers were low, however, indicating that these noncirrhotic patients had in the past had HB virus (HBV) infection with no residual chronic B hepatitis. Analysis of the grades of anaplasia of cancer tissue demonstrated an inverse correlation between the degree of fibrosis and grade of anaplasia, i.e., the more advanced the fibrosis, the less anaplastic the cancer. These data suggest that HCC arising in highly cirrhotic livers and in noncirrhotic livers have different pathogenetic backgrounds, and that HBV infection, even though transient, has a certain role in hepatocarcinogenesis. The generally held conjecture that HCC in a noncirrhotic liver is caused by nonviral carcinogens and HCC arising on the ground of cirrhosis is due to HBV seems untenable in such a simple concept. (Author abstract) (27 Refs)

11. CELL MARKERS IN HAIRY CELL LEUKEMIA STUDIED IN CELLS FROM 51 PATIENTS.

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Blood; 59(1):52-60 1982

To determine the maturation arrest of the neoplastic cells of hairy-cell leukemia (HCL) and the spectrum of the surface markers on these cells, a series of 51 patients with this disease was studied. The cells of all but two of the patients showed monoclonal surface Ig with respect to light chains. In about one-third of the cases, only gamma heavy chain determinants were present on the cells; the majority carried multiple heavy chain determinants as documented by the application of different fluorochromes. Two patients each showed two different clones of cells, both of the same light chain type. In one of these two patients, two paraproteins were present in the serum. Intracytoplasmic Ig was found in only 4 of 39 cases, in all instances being IgM. All cases studied concerned cells with FcIgG receptors; however, the density of this receptor varied. FcIgM receptors also showed a spectrum of density, with some cases showing very few FcIgM-positive cells. Receptors for C3 were not observed on the hairy cells. Serum immunoglobulin levels were normal or increased. Paraproteins were found in the sera of 4 of 38 patients. These data suggest that HCL is a neoplasm of B lymphocytes. The neoplastic cells are probably arrested at a more mature stage than the cells of chronic lymphocytic leukemia. The multiple isotypes on the cells indicate a block at the 'switch' phase from the small mu-carrying lymphocyte to the larger Ig-producing lymphocyte or plasma cell. (Author abstract) (42 Refs)

12. T-CELL GROWTH FACTOR-MEDIATED PROLIFERATION OF LYMPHOCYTES FROM A T-CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENT LACKING MITOGEN AND ALLOANTIGEN RESPONSIVENESS.

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Clin Exp Immunol; 43(2):302-310 1981

Peripheral blood lymphocytes (PBL) of chronic lymphocytic leukemia of T cell origin (T-CLL), which were unresponsive to mitogens and had negligible stimulator and responder capacities in mixed lymphocyte cultures (MLC), were induced to proliferate by human T cell growth factors (TCGF). Long-term T-CLL PBL cultures were obtained in the presence of TCGF. T-CLL PBL obtained from a female patient (30 yr old) showed no 3H-thymidine (3HTdR) incorporation when stimulated with various concentrations of phytohemagglutinin (PHA), Concanavalin A, or pokeweed mitogen. The T-CLL PBL exhibited greatly reduced responder and inducer capacities (12% and 14% that of normal sheep RBC rosette-forming cells, respectively). TCGF-1 had the strongest growth-promoting activity and was used as a standard (1.0 growth-promoting unit). TCGF-1,-2, and-3 contained 0.52, 0.29, and 0.33 growth-promoting units, respectively. PHA stimulated proliferation of T-CLL cells in the presence of TCGF-1. Both TCGF-3 and-4 also induced and maintained T-CLL PBL proliferation in the presence of PHA, but at considerably lower rates than those produced in the presence of TCGF-1 and-2. In MLC, addition of TCGF-4 resulted in a four-fold increase in 3H-TdR incorporation in T-CLL PBL after stimulation with lymphocytes from a normal donor (C). Lymphocytes from donor C showed an 80-fold increase in 3H-TdR incorporation when cultured with T-CLL PBL in the presence of TCGF-4. The results indicated that the lack of response to mitogens and alloantigens of the T-CLL PBL can be attributed to the failure of these cells to produce TCGF upon activation. (36 Refs)

13. ANALYSIS OF THE PEANUT AGGLUTININ-BINDING SITE AS A DIFFERENTIATION MARKER OF NORMAL AND MALIGNANT HUMAN LYMPHOID CELLS.

Galili U, Galili N, Or R, Polliack A
Dept. Haematology, Hadassah Univ. Hosp., Jerusalem, Israel
Clin Exp Immunol; 43(2):311-318 1981

Human lymphoid cells obtained from bone marrow, thymus, spleen, and lymph node tissues were studied for their capacity to bind fluorescein-bound (FITC) peanut agglutinin (PNA). The PNA-binding capacity of a variety of leukemic and cultured human lymphoblastoid cells was examined to determine if this membrane characteristic can be used to distinguish subsets of leukemic cells. Of normal cells from lymphoid organs studied, only thymocytes bound PNA. Peripheral blood lymphocytes did not bind PNA. RBC E-rosetting thymocytes bound PNA, whereas prothymocytes that did not form E rosettes did not bind PNA. Fetal splenic lymphocytes, like their adult counterparts, lacked PNA-binding capacity. Lymphoblastoid cell lines were examined for staining with FITC PNA. The only T-derived line that exhibited strong PNA binding

was acute lymphoblastic leukemia (ALL)-derived Be13 cells; Hodgkin's disease-derived HD-MAR cells that readily form E rosettes interacted very weakly with PNA. Other T lines that express human T antigen lacked PNA-binding ability. All B cell-derived cell lines originating from African or American type Burkitt lymphoma exhibited strong specific binding of FITC-PNA. Other B-cell lines also exhibited PNA binding. Leukemic cells from 3/15 ALL patients, 3/3 with non-Hodgkin's lymphoma, and 1/1 with hairy cell leukemia exhibited PNA binding. Cells from 3/11 acute myeloid leukemia patients showed partial PNA binding. No leukemic cells from patients with chronic lymphocytic (9 patients) or chronic myeloid (4) leukemia bound FITC PNA. The usefulness of PNA as a differentiation marker in malignant cells is discussed. (31 Refs)

14. LYSIS OF TUMOR BIOPSY CELLS BY AUTOLOGOUS T LYMPHOCYTES ACTIVATED IN MIXED CULTURES AND PROPAGATED WITH T CELL GROWTH FACTOR.

Vanky F, Gorsky T, Gorsky Y, Masucci M, Klein E
Dept. Tumor Biology, Karolinska Inst., S-104 01, Stockholm 60, Sweden
J Exp Med; 155(1):83-95 1982

Lymphocytes of patients activated in mixed lymphocyte culture (MLC) lysed allogeneic third-party cells and in some cases also lysed autologous tumor cells. Allogeneic but not autologous phytohemagglutinin (PHA) blasts were also damaged by these effectors. The cytotoxic potential of MLC-activated lymphocytes from healthy donors was similar: allogeneic tumor and PHA blasts but not autologous PHA blasts were lysed. The cytotoxicity of lymphocytes activated in autologous tumor cells were specific for the stimulator because they acted only on the autologous tumor cells. Results obtained in cold target competition assays suggested that activated lymphocytes lyse the third party tumor targets because of alloantigen recognition and in MLC, several different sets of alloreactive cytotoxic lymphocytes are present simultaneously. There all-reactive cells are different to those that act on autologous tumor cells. The lysis of allogeneic tumor cells by lymphocytes of the patient is probably not due to recognition of cross-reacting tumor related antigens, and the antitumor cytotoxicity of the patients' MLC-activated lymphocytes is due to specifically reacting cells. (40 Refs)

15. EFFECT OF DIFFERENT EPSTEIN-BARR VIRUS-DETERMINED ANTIGENS (EBNA, EA, AND VCA) ON THE LEUKOCYTE MIGRATION OF HEALTHY DONORS AND PATIENTS WITH INFECTIOUS MONONUCLEOSIS AND CERTAIN IMMUNODEFICIENCIES.

Szigeti R, Masucci MG, Henle W, Henle G, Purtilo D, Klein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Clin Immunol Immunopathol; 22(1):128-138 1982

Leukocytes from healthy Epstein-Barr virus (EBV)-seropositive (SP) subjects show significant migration inhibition (LMI) with EBNA (EBV-determined nuclear antigen)-containing extracts derived from nonproducer, EBV-genome-carrying cells, or presented in the form of partially purified EBNA-preparations. Additional EBV antigens, EA and VCA, presented in the form of induced cell extracts do not add any measurable increase to their response. Leukocytes from acute infectious mononucleosis (IM) patients, on the other hand, do not respond to EBNA, but they show a good response to induced EA- or EA and VCA-containing cell extracts. This is in accordance with known differences in EBV-antibody pattern in healthy SPs as contrasted to acute IM patients. Leukocytes from chronic mononucleosis patients resemble those from acute IM patients in their preferential EA/VCA and deficient EBNA response in the LMI test. Cells from four X-linked lymphoproliferative disease (XLP) patients showed complete absence of reactivity to PHA and to EBV antigens in the LMI test, showing a general defect in cell-mediated immune responses. Leukocytes from a group of patients with lymphoproliferative malignancies in remission and elevated EBV-antibody titers showed a variety of responses, resembling normal SP donors, or IM patients, or showing a complete unresponsiveness in the LMI test. (Author abstract) (41 Refs)

16. RELATIONSHIP BETWEEN LYMPHOCYTE PROLIFERATION AND MIGRATION INHIBITORY FACTOR PRODUCTION IN RESPONSE TO AUTOLOGOUS TUMOR EXTRACT IN CANCER PATIENTS.

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Gan; 72(6):988-991 1981

In forty-nine patients with various carcinomas, cell-mediated immune response to 3M KCl extract of autologous tumor was studied with the use of both lymphocyte proliferation (LP) assay and m acrophage migration inhibition (MMI) assay simultaneously. There was no correlation between stimulation index in LP assay and migration index in MMI assay in these simultaneous tests. The results of this study indicate dissociation between cell proliferation and migration inhibitory factor production of lymphocytes in response to autologous tumor extract in patients with various carcinomas. (Author abstract) (15 Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

17. VALUE OF PLASMA ALPHA-1-ACID GLYCOPROTEIN ASSAY IN THE DETECTION OF HUMAN COLORECTAL CANCER: COMPARISON WITH CARCINOEMBRYONIC ANTIGEN.

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JNCI; 68(1):75-79 1982

Plasma specimens assessed for carcinoembryonic antigen (CEA) in the clinical laboratory for the detection of colorectal cancer were simultaneously assayed in our laboratory for alpha-1-acid glycoprotein (alpha1AG), by means of a solid-phase enzyme-linked immunosorbent assay we developed. In 28 patients with colorectal cancer of Dukes A, B, and C classes, elevated levels of alpha1AG were seen in 12 and of CEA in 8. In 44 patients with distant metastasis (Dukes D lesions), elevated plasma levels of alpha1AG were seen in 29 and of CEA in 34. No statistical differences in the detection rate were found among these markers in these two groups of patients. In 33 cases of non-neoplastic disease involving the large bowel, elevated plasma levels of alpha1AG were seen in 6, and elevated CEA levels were seen in 7. There was no statistical difference of false positive rates among these two markers. Elevated plasma levels of either CEA or alpha1AG were found in 57 cases of colorectal cancer. This preliminary study suggests

that the sensitivity of the plasma alpha1AG assay is similar to that of the CEA assay in the detection of colorectal cancer. The combination of these two assays increases the detection rate of colorectal cancer significantly. (Author abstract) (32 Refs)

18. PREGNANCY-ASSOCIATED AND PLACENTAL PROTEINS (SP1, HCG, PP5, ALPHA2-PAG) IN PATIENTS WITH TROPHOBLAST TUMORS.

Than G, Csaba I, Szabo D, Karg N, Gocze P
Noi Klinika, Pecsi Orvostudomanyi Egyetem, Pecs, Hungary
Orv Hetil; 122(43):2650-2654 1981

The serum levels of specific beta-1 glycoprotein (SP1), beta subunit of human chorionic gonadotropic (HCG), placental protein 5 (PP5) and pregnancy-associated alpha2-glycoprotein (alpha2-PAG) were monitored in 41 patients with trophoblast tumors. Hydatid mole was diagnosed in 26 patients, chorioadenoma in 8 and choriocarcinoma in 7. Twenty-six patients were pretreated at the beginning of the monitoring. The HCG levels were elevated in 35 patients, the SP1 levels in 36, and the alpha2-PAG levels in 29. PP5 was found only in 11 patients, all with hydatid moles. The SP1 and HCG levels decreased along with clinical improvement to disappear altogether in remission after several mo. Elevated HCG levels persisted longer in the majority of the cases. Both marked were found to be sensitive indicators of residual tumor activity and of recurrence several mo before recurrences became clinically evident. Only SP1 or HCG was found in the sera of some patients during the monitoring, which indicates the importance of the simultaneous determination of the SP1 and HCG levels. The alpha2-PAG levels were positively correlated with the clinical course of the disease, as well as with the changes in the HCG and SP1 levels, which indicates that alpha2-PAG is a lesser practical significance than HCG and SP1. (34 Refs) (In HUN)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

19. THE CLINICAL SIGNIFICANCE OF TISSUE POLYPEPTIDE ANTIGEN (TPA) IN THE URINE OF BLADDER CANCER PATIENTS.

Kumar S, Costello CB, Glashan RW, Bjorklund B
Paediatric Oncology Lab., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England
Br J Urol; 53(6):578-581 1981

A 2-stage study has been carried out to evaluate the usefulness of urinary tissue polypeptide antigen (TPA) levels in patients with bladder cancer as an adjunct to the routine procedures for detection of bladder tumors. Two-hr urine samples were collected from 83 bladder cancer patients and normal individuals for the first part of the study, 24-hr samples from 54 patients and normal individuals for the second part. Urinary TPA was determined using radioimmunoassay. In 2-hr samples there was no significant difference in the amounts of TPA/I in any of the groups. In contrast, the TPA results of 24-hr urine samples (n = 54) were markedly different from 2-hr samples, and the former correlated very well with the presence or absence of bladder cancer. A reason for this difference may be circadian rhythm effects. (Author abstract) (15 Refs)

20. CAN ACUTE PHASE REACTANTS DISTINGUISH BENIGN AND MALIGNANT DISEASE OF THE UPPER GUT?

Grindulis KA, Forster PJ, Hubball S, McConkey B
Dudley Road Hosp., Dudley Road, Birmingham, B18 7QH, England
Clin Oncol; 7(4):345-350 1981

Four 'acute phase reactants' (C-reactive protein, alpha-I-antitrypsin, haptoglobin, and orosomucoid) were measured in 107 patients undergoing upper gastro-intestinal endoscopy. There was a significant increase (p less than 0.05; Mann-Whitney U test) in the concentrations of all four proteins in patients with carcinoma when compared to those with normal findings or scarring of stomach or duodenum. Though the patients with malignancy also had higher mean acute phase reactant concentrations than those with peptic ulcer and non-malignant inflammation, the difference did not reach statistical significanc e. Despite these differences, the scatter of concentrations reduced the value of acute phase reactants as discriminators of benign and malignant disease in the individual case. Recurrence of raised concentrations after reduction with treatment would suggest an increase in residual tumor mass and the use of these proteins to indicate recurrent malignancy warrants further study. (Author abstract) (9 Refs)

21. STUDY OF HYDROXYPROLINE EXCRETION IN PATIENTS WITH PROSTATIC CANCER.

Romics I, Budavari I, Kisbenedek L, Balogh F
Dept. Urology, Inst. Pathophysiology, Semmelweis Univ. Medical Sch., Budapest, Hungary
Int Urol Nephrol; 13(3):275-278 1981

Urinary hydroxyproline (HP) concentrations were measured in 36 patients with prostatic cancer (PC). In 24 of the patients no radiographic evidence of deposits was found during the period of study; in 12 patients skeletal metastases were demonstrable by radiography. Fourteen patients with no malignant disease served as controls. HP was measured in 24-hr collected urine and in blood sera. Excretion was abnormally high (2.86 +-0.40 mg/24 hr) in 8/24 patients who had PC but no metastases. Skeletal radiography was repeated 6 mo later in order to clarify the origin of increased excretion. Serum HP levels were in the normal range throughout. Urinary HP excretion of the controls, measured in samples from 24-hr urine, was 1.04 +-0.16 mg/24 hr. In patients with PC and no metastases, the mean HP value was 1.80 +-0.81 mg/24 hr. The upper limit of the normal range is 2 mg/100 ml. Seven mo later bone x-ray studies revealed skeletal metastases in 7/8 patients with urinary HP values greater than 2 mg/24 hr. The mean HP excretion was 6.25 +-2.25 mg/24 hr in six untreated patients who had skeletal metastases at the beginning of the study. Results showed a significant difference in the HP values for patients with PC and controls. Primary tumors and malignant metastases to the skeletal system are associated with an increase in the urinary level of HP. Metastases of PC are prevalently skeletal. Measurement of HP urine levels provides a reliable and practical test for follow-up of the malignant prostatic process and response to therapy. (10 Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

22. GAMMA-GLUTAMYL TRANSPEPTIDASE IN A NEWLY ESTABLISHED CELL LINE FROM HUMAN RENAL CARCINOMA, OUR-10.

Hada T, Higashino K, Yamamoto H, Okochi T, Sumikawa K, Watanabe S, Matsuda M, Osafune M, Kotake T, Sonoda T

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Gan; 72(6):842-847 1981

A newly established cell line, OUR-10, from human renal carcinoma seems to have the same gamma-glutamyl transpeptidase as the novel one which was found recently in renal carcinoma tissue; the enzymic properties such as electrophoretic mobility, Km value, mol wt, thermostability, the effects of urea, sodium dodecyl sulfate and sulfhydryl reagents, the effects of amino acids, cations and EDTA, and the binding behavior to a concanavalin A-Sepharose column were the same as those of the novel gamma-glutamyl transpeptidase found in renal carcinoma tissue. The immunological properties of the gamma-glutamyl transpeptidase (GGTP) of OUR-10 examined by inhibition tests and tests of cross-reactivity with anti-normal kidney GGTP antibody were also the same as those of the novel gamma-glutamyl transpeptidase. These results may mean that the novel gamma-glutamyl transpeptidase originates from the cancer cells, and can be used as a marker for identification of this cell line, OUR-10. (Author abstract) (19 Refs)

23. HISTOCHEMICAL LOCALIZATION OF CATHEPSIN B AT THE INVASION FRONT OF THE RABBIT V2 CARCINOMA.

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Div. Cancer Res., Inst. Pathology, Univ. Zurich, Zurich, Switzerland

Lab Invest; 45(6):587-596 1981

To clarify the role of cathepsin B in tumor invasion, the enzyme was visualized in tissue frozen sections of the subcutaneously growing rabbit V2 carcinoma. Localization of cathepsin B was achieved by immunofluorescent staining and by enzyme histochemistry. For the former approach, a sheep antiserum was raised against purified cathepsin B from rabbit liver. The antibodies, isolated by immunoadsorption, reaction monospecifically with rabbit liver cathepsin B in Ouchterlony double diffusion and in immunoelectrophoresis. In the enzyme histochemical assay, Z-Ala-Arg-Arg-methoxynaphthylamide was used as fluorogenic substrate and nitrosalicylaldehyde as coupling agent. With both methods, cathepsin B was found to be localized within fibroblasts and leukocytes assembled at the tumor invasion front. In addition, immunofluorescent staining demonstrated the occurrence of the enzyme in the extracellular matrix surrounding tumor cell clusters. Carcinoma cells always remained unstained. The conclusion is drawn that cathepsin B is chiefly produced by host cells which are stimulated to increase synthesis and to release the enzyme under the influence of the tumor. A dual function can be ascribed to cathepin B concentrated in the vicinity of the tumor: it operates intracellularly (in host cells) through degradation of endocytosed protein and extracellularly through activation of collagenase. The resulting lytic action on host structures appears to be a prerequisite for local spread of the V2 carcinoma. (Author abstract) (58 Refs)

24. HETEROGENEITY IN SURFACE ANTIGEN AND GLYCOPROTEIN EXPRESSION OF CELL LINES DERIVED FROM DIFFERENT MELANOMA METASTASES OF THE SAME PATIENT. IMPLICATIONS FOR THE STUDY OF TUMOR ANTIGENS.

Albino AP, Lloyd KO, Houghton AN, Oettgen HF, Old LJ
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021

J Exp Med; 154(6):1764-1778 1981

Three melanoma cell lines (DX-1,-2, and-3) derived from separate metastatic foci of patient DX (a 70 yr old woman) were examined for phenotypic differences in growth, morphology, and expression of cell surface antigens and glycoproteins. DX-1 and-2 accumulated visible pigment; DX-3 cell appeared unpigmented. DX-2 and-3 cell lines grew as attached monolayers, while DX-1 showed a marked tendency to grow in suspension after initial attachment as microcolonies of rounded cells. Only DX-1 and-3 cells expressed D-locus human WBC antigen surface antigens. Less marked but characteristic differences were detected in the expression of other cell surface antigens. DX-2 and-3 exhibited similar profiles of cell surface glycoproteins in the high mol wt region, with 90,000 and 120,000 mol wt components being particularly prominent. DX-2 had an additional prominent component of 60,000 mol wt which was only weakly labeled in DX-3. DX-3 exhibited two major glycoproteins in the low mol wt region of 32,000 and 27,000. Only one major glycoprotein of 90,000 mol wt was labeled in DX-1 monolayer cells. Sera from patient DX reacted only with surface antigen of autologous DX-2; the highest reactivity was in the IgG fraction. The time-course of DX autologous reactivity was examined. Absorption analysis indicated that the DX-2 antigen was a class 1 melanoma antigen; the antigen was also detectable in much lower but demonstrable amounts in DX-1 and-3 cells. No other cell type tested exhibited the class 1 DX melanoma antigen. (21 Refs)

25. SURFACE EXPRESSION OF ALIEN HYBRID IE/C ANTIGENS ON THE RETICULUM CELL SARCOMA OF SJL/J MICE.

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Transplant Proc; 13(4):1833-1836 1981

The biologic and molecular nature of the murine response elicited by spontaneous tumors in SJL/J mice was investigated. Reticulum cell sarcoma (RCS) tumors expressed IE/C antigens that are alien to the host SJL/J; the antigens are not normal membrane constituents of host SJL/J cells. Investigations demonstrated the expression of alien H-2d specificities on RCS cells by serologic, cell-mediated, and immunological assay The detection of alien H-2 specificities on RCS tumor cells varied with different assays according to the origin of RCS tumor cells. SJL/J anti-DBA/2 lymphocytes (from 4-day mixed lymphocyte reaction) bound H-2d and RCS tumor cells but not SJL/J or cells from other haplotypes. The syngeneic antitumor lymphocytes apparently have receptors for tumor associated antigen cross-reactive with H-2d specificities. Antigens recognized by the antitumor lymphocyte were analyzed using recombinant strains of mice. RCS antigens expressed hybrid Ia antigens encoded by the IE/C subregion of the major histocompatibility complex. The Ia.7 specificity was expressed on the component of hybrid Ia molecules regardless of haplotype. Experiments suggest that the RCS tumors absorbed the Ia.7 specificity. SJL/J and C57BL/6 (lacking Ia.7 specificity) did not absorb the cytotoxic activity. Results suggest that RCS

tumors express on their surface IE/C antigens serologically identical to IE/C antigens of other H-2 haplotypes. (13 Refs)

26. METHODS FOR PRODUCTION OF MONOCLONAL ANTIBODIES WITH SPECIFICITY FOR HUMAN LUNG CANCER CELLS.

Minna JD, Cuttitta F, Rosen S, Bunn PA, Carney DN, Gazdar AF, Krasnow S
NCI-Veterans Admin. Branch, Div. Cancer Treatment, NCI, Washington, DC
In Vitro; 17(12):1058-1070 1981

We have developed a screening strategy and technology to produce monoclonal antibodies with specificity for human lung cancer cells. Mice and rats were immunized with well-characterized tissue culture lines of human small cell lung cancer (SCLC), mouse myeloma x spleen hybrids formed by the technique of Kohler and Milstein, and the resulting culture fluids were screened for antibody binding phenotype using a radioimmunoassay. To facilitate testing large numbers of culture fluids, a 96-well, microtiter based, re-usable, replicating device was designed. Using this, many hybridoma culture fluids were replica plated for antibody binding tests on a series of human target cell plates. Hybrids producing antibodies that reacted with the immunizing SCLC line and another independent SCLC line, but not with autologous B-lymphoblastoid cells derived from one of the patients, were identified, selected, and then repeatedly recloned using the same screening strategy. With this technology, hybridomas representing less than 0.5% of all hybrids generated could be isolated and stable antibody producing cultures derived. Such antibodies reacted with a panel of well-characterized SCLC lines and SCLC samples taken directly from patients but not with a variety of normal tissues. Using these antibodies we can demonstrate: tumor cell contamination of bone marrow specimens, marked heterogeneity of antigen expression on cells within individual SCLC lines and individual patients, and inhibition of clonal growth of SCLC lines in soft agarose assays. All of these findings have potential clinical and cell biologic application. (Author abstract) (50 Refs)

27. THE REACTION SPECIFICITY OF VARIOUS MONOCLONAL ANTIBODIES AND CELLULAR ORIGIN AND DIFFERENTIATION OF CULTURED CELL LINES DERIVED FROM HUMAN LEUKEMIAS AND LYMPHOMAS.

Tobinai K, Hirose M, Minato K, Shimoyama M
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Jpn J Clin Oncol; 11(3):469-479 1981

Human hemopoietic tumor-cell lines (6 T-cell; 10 B-cell; 5 non-T, non-B-cell; 2 myeloid; 2 monocytoid) were grown exponentially, and their reactions to 12 monoclonal antibodies (OKT 3, OKT 4, OKT 6, OKT 8, OKI 1, OKM 1, anti-Leu-1, 10.2, (antihuman Lyt 2), 9.6 (antihuman Lyt-3), anti-B1, J5, anti-Mo 1) were evaluated by indirect immunofluorescence assay and by rosette-forming capacity with sheep erythrocytes, human T-lymphocyte antigen, Ia-like antigen, and surface immunoglobulins. The reactivities of the monoclonal antibodies were highly specific against cultured leukemia and lymphoma cell lines, with a few exceptions, which are described. The titer of the antibody differed among the cell lines, indicating that while use of the monoclonal antibodies specific for certain differentiation antigens may be useful for elucidating the cellular origin, stage of differentiation, and subset identification of human hemopoietic tumor cells, the titration of each monoclonal antibody requires the use of several cultured cell lines in order to determine an appropriate concentration for clinical use. (42 Refs)

28. MONOCLONAL ANTIBODY-RICIN A CHAIN CONJUGATE SELECTIVELY CYTOTOXIC FOR CELLS BEARING THE COMMON ACUTE LYMPHOBLASTIC LEUKEMIA ANTIGEN.

Raso V, Ritz J, Basala M, Schlossman SF
Div. Pharmacology, Sidney Farber Cancer Inst., Boston, MA, 02115
Cancer Res; 42(2):457-464 1982

The toxic subunit of ricin has been conjugated by a disulfide bone to a monoclonal murine antibody (J-5) specific for the common acute lymphoblastic leukemia antigen (CALLA) expressed on human lymphoblastic leukemia cells. Both the monoclonal antibody and ricin A chain retained their original biological activity after conjugation. The ricin A chain antibody-combining site attached to the membrane of CALLA-bearing cells, whereupon both components of the molecule, antibody and A chain, could be detected using fluorescein-labeled antibody probes directed against either mouse F(ab')2 or ricin A chain. This conjugate proved to be a potent cytotoxin for CALLA-positive Nalm-1 cells growing in vitro and produced 50% inhibition of proliferation at levels of 2 x 10(-10) M. CALLA-negative cell lines were unaffected until levels of conjugate approached 10-6 M. When tested for cytotoxic action on Nalm-1 cells, the composite conjugate molecule was at least 2,000x more effective than J-5 antibody alone, ricin A chain alone, or a noncovalent mixture of these components. Cytotoxicity of the conjugate could be blocked completely by addition of antibodies specific for either mouse Ig or ricin A chain. Direct comparison of the in vitro cytotoxity of CALLA-directed univalent Fab versus bivalent F(ab')2 carriers of ricin A chain revealed 70-fold greater efficacy for the latter conjugate. This differential could not be accounted for by differences in A chain activity or binding affinity for the cell membrane but appeared related to the ability of the multivalent agent to induce modulation and internalization of CALLA determinants. No overt toxic effects were noted when th e F(ab')2-A chain conjugates was administered iv to rabbits at levels as high as 20 mg/kg single injection or 5 mg/kg for 5 days. The unique specificity characteristics and high potency of this cytotoxic conjugate indicate that it has significant therapeutic potential for the treatment of CALLA-bearing human leukemias and lymphomas. (37 Refs)

29. SPECIFIC CYTOTOXICITY AGAINST AUTOLOGOUS TUMOUR AND PROLIFERATIVE RESPONSES OF HUMAN LYMPHOCYTES GROWN IN INTERLEUKIN 2.

Vose BM, Bonnard GD
Dept. Immunology, Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England
Int J Cancer; 29(1):33-39 1982

Peripheral blood lymphocytes of cancer patients were sensitized in vitro to autologous tumor cells in mixed lymphocyte-tumor culture (MLTC). Blast cells were isolated on discontinuous Percoll gradients from MLTC which showed significant stimulation of [3H]-thymidine incorporation. Cultured T cells (CTC) were derived from these blasts by growth in conditioned medium containing interleukin-2 (IL-2) and maintained for up to 51 days by repeated feeding with IL-2 and in some cases by addition of irradiated allogeneic blood mononuclear cells as 'fillers.' These cultures showed specific cytotoxic reactivity against autologous tumor, and in only a few cases was natural

killing (NK) of K562 cells apparent. Restimulation of CTC with tumor was measured in primed lymphocyte tests (PLT). Increased uptake of [3H]-thymidine was found upon stimulation by autologous tumor and allogeneic tumor of the same site and histology, but there was no response to non-related tumors or to a panel of allogeneic lymphocytes. No sensitization to autologous HLA D/DR could be detected by restimulation or cytotoxicity against monocytes in the majority of cases. These data suggest that, by careful selection of sensitized blasts from MLTC, it is possible to obtain CTC with both helper (proliferative) and cytotoxic T cells and that such CTC have specific reactivity against tumor cells. These cellular reagents will be useful in defining the antigenicity of human neoplasms and possibly in therapy. (Author abstract) (39 Refs)

30. USE OF CAPILLARY TUBE LEUKOCYTE ADHERENCE INHIBITION FOR THE DETECTION OF TUMOR-SPECIFIC IMMUNE RESPONSE.

Myers WL, O'Keefe ML
Dept. Medical Microbiology and Immunology, Southern Illinois Univ. Sch. Medicine, P.O. Box 3926, Springfield, IL, 62708
Immunol Commun; 10(4):407-416 1981

The tumor-specific immune response of A/J mice was determined at various times after subcutaneous injection with a transplantable spindle-cell sarcoma (SaI) using a leukocyte adherence inhibition (LAI) assay carried out in capillary tubes. Solubilized antigens prepared by 3M KCl extraction of the specific tumor, other transplantable tumors and normal A/J liver were used in the evaluation of LAI re activity. The assay was found to be capable of detecting a significant antitumor response before the subcutaneous tumors became detectable by palpation. The response remained significant until the tumors were greater than 25 mm in diameter. Responsive cell populations did produce an active supernatant, indicating the possible presence of a lymphokine and/or specific cytophilic antibody. (Author abstract) (19 Refs)

31. ANTITUMOR IMMUNITY IN B-LYMPHOCYTE-DEPRIVED MICE. II. IN VITRO STUDIES.

Brodt P, Gordon J
Dept. Surgery, Div. Surgical Res., McGill Univ., Donner Building, 740 Docteur Penfield Ave., Montreal, Quebec H3A 1A4, Canada
Cell Immunol; 65(1):20-32 1981

In a previous publication, we reported that B-lymphocyte-deprived mice possess a heightened in vivo resistance to a methylcholanthrene-induced syngeneic fibrosarcoma. The present in vitro study has disclosed that spleens of such mice possess a significantly higher cytotoxic activity against the same tumor compared to normal rabbit globulin-injected control animals, and that this increase cannot be accounted for by the mere elimination of B lymphocytes. The cell mediating this response was found to be a natural-killer-like cell on the basis of its organ distribution, its full activation without immunization, its target specificity shown directly and by cold target inhibition experiments, and by its surface markers. It is suggested that this increased activity, which does not appear to decline with age, may be responsible for the heightened in vivo antitumor resistance of T mice. (Author abstract) (32 Refs)

32. THE EFFECT OF LOCAL TUMOR IRRADIATION ON CELL-MEDIATED TUMOR IMMUNITY IN TUMOR-BEARING MICE.

Yamashita T
Dept. Radiology, Jikei Univ. Sch. Medicine, Jikei, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(9):887-893 1981

The effect of inoculation of spleen lymphocytes derived fro tumor-bearing mice irradiated locally to tumor on the ability to suppress tumor incidences of syngeneic mice was studied on sarcoma to be grown in the leg of BALB/c mice using Winn assay. The tumor-specific cytotoxicity of spleen lymphocytes was most distinct when the spleen lymphocytes taken out on the 7th day after irradiation with the dose of 1,000 rad or more from the tumor-bearing mice locally irradiated on tumors of the size of 8 mm in diameter was given, and even when the 15 mm diameter's tumor was used, the cytotoxicity of spleen lymphocytes was activated after x-irradiation of the tumor. Suppression of tumor incidence was clearer in the group inoculated tumor cells and lymphocytes in the ratio of 1:200 compared with the ratio 1:50. These results suggest that tumor specific immunopotential can be obtained by local x-irradiation to tumors. (Author abstract) (26 Refs) (In JPN)

* U. S. GOVERNMENT PRINTING OFFICE : 1982—361-647/119

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. CIRCULATING CEA LEVELS IN PATIENTS WITH FULMINANT HEPATITIS.

George PK, Loewenstein MS, O'Brien MJ, Bronstein B, Koff RS, Zamcheck N

(c/o Zamcheck) Mallory Gastrointestinal Res. Lab., Boston City Hosp., Boston, MA, 02118

Dig Dis Sci; 27(2):139-142 1982

CEA levels were determined in blood specimens from 14 persons suffering from ful minant hepatitis. Values ranged from 1.9 to 21 ng/ml with a mean of 7.0 ng/ml. All except one patient had a CEA level greater than 2.5 ng/ml, but only three exceeded 10 ng/ml. There was no correlation between single CEA levels and prognosis, routine liver chemistries, or histopathologic characterization of hepatic tissue obtained at postmortem examination. These data show that patients with fulminant hepatitis commonly had increased circulating levels of CEA, but these elevations were far less than may be found in patients with hepatic metastases. In severe hepatic dysfunction reduced hepatic clearance of CEA may be responsible for the increased levels. (Author abstract) (19 Refs)

2. A PROSPECTIVE ANALYSIS OF LABORATORY TESTS AND IMAGING STUDIES TO DETECT HEPATIC LESIONS.

Kemeny MM, Sugarbaker PH, Smith TJ, Edwards BK, Shawker T, Vermess M, Jones AE

(c/o Sugarbaker), NIH, Building 10, Room 10N116, Bethesda, MD, 20205

Ann Surg; 195(2):163-167 1982

A prospective study of ability of laboratory tests and liver imaging tests to detect hepatic metastases was performed. Eighty patients at risk for hepatic metastases but without clinical evidence of disease were tested with 13 laboratory tests and 3 liver imaging tests. No single laboratory test had greater than 65% accuracy in the detection of hepatic lesions. No combination of the laboratory tests increased this accuracy. If the laboratory tests were used with one of the liver imaging tests, the accuracy was improved in some combinations to 76%. The CEA assay when analyzed in patients with colorectal primaries had an accuracy of 79%. The results show that the laboratory tests alone are not sufficiently accurate to detect liver metastases. Additional accuracy can be obtained by the combined use of a single liver imaging test and selected laboratory tests. Use of all the liver imaging tests and laboratory tests lowers the accuracy and increases the expense and thus is unnecessary. (Author abstract) (22 Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

3. COMPARATIVE ESTIMATION OF THREE RADIOIMMUNOASSAY KITS FOR HUMAN PROSTATIC ACID PHOSPHATASE.

Wakabayashi K, Sugiyama Y, Shida K

Inst. Endrocrinology, Gunma Univ., Showa-machi 3-39-15, Maebashi, 371, Japan

Prostate; (Suppl1):71-78 1981

Three commercially available prostatic acid phosphatase (PAP) radioimmunoassay (RIA) kits, PAP EIKEN' (EIK: Eiken ICL, Tokyo), Gamma Dab PAP RIA kit (CLA: Clinical Assays, Division of Travenol, Cambridge, Massachusetts), and RIA-Quant. P.A.P. (MKT: Mallinckrodt, St. Louis, Missouri), were compared using serum samples from normal subjects and urological patients with nonprostatic disease. All three kits could measure PAP above normal levels in serum samples with reasonable reproducibility and reliability. Enzymatic activity of samples correlated well with immunoreactivity. Assay results from sera with normal levels of PAP were not always in agreement; data obtained with the CLA kit did not correlate with those obtained with the other two kits. Although some improvement in sensitivity of CLA and MKT kits would be useful, the results, combined with the observed stability of immunoreactivity of PAP, indicate a diagnostic usefulness for these kits in prostatic cancer. (15 Refs)

4. COMPARISON OF ENZYME-LINKED IMMUNOSORBENT ASSAY AND RADIOIMMUNOASSAY FOR PROSTATE-SPECIFIC ACID PHOSPHATASE IN PROSTATIC DISEASE.

Griffiths J, Rippe DF, Panfili PR

Sumerlin Memorial Pathology Lab., Donald N. Sharp Memorial Community Hosp., 7901 Frost St., San Diege, CA, 92123

Clin Chem; 28(1):183-186 1982

We compared results by an enzyme-linked immunosorbent assay (ELISA) with those by a standard radioimmunoassay (RIA) for detection and quantitation of prostate-specific acid phosphatase (EC 3.1.3.2) in serum. Control subjects, patients with benign prostatic hyperplasia, and patients in all four clinical stages of prostatic adenocarcinoma were tested. The upper limit of normal (95% of the population) by the ELISA was 2.0 ug/L, and by the RIA was 2.2 ug/L. In prostatic adenocarcinoma Stage I (not detectable by digital rectal examination), ELISA was slightly more sensitive than RIA, but sensitivity was still relatively low (20%). As tumor mass increased (Stages II through IV), the frequency of increased concentrations of prostatic acid phosphatase in serum also increased. We confirmed this increase in circulating enzyme in some cases of benign prostatic hyperplasia and suggest that this finding is related to either acinar cytolysis or an increase in acini size and number. Although prostate-specific acid phosphatase is not a cancer-specific enzyme, we conclude that its measurement may be of considerable value in monitoring prostatic disease. (Author abstract) (12 Refs)

5. BONE MARROW ACID PHOSPHATASE BY COUNTERIMMUNE ELECTROPHORESIS: PRE-TREATMENT AND POST-TREATMENT CORRELATIONS.

Schellhammer PF, Warden SS, Wright GL, Sieg SM
Dept. Urology, Eastern Virginia Medical Sch., Norfolk, VA
J Urol; 127(1):66-68 1982

The value of bone marrow acid phosphatase in the staging of prostatic cancer has been a controversial issue. A number of investigators have concluded that the enzymatic determinations of bone marrow acid phosphatase are inaccurate because of lack of specificity. The introduction of the immune methods for measuring acid phosphatase has revived interest in the role of immune bone marrow acid phosphatase in pre-treatment staging. Fifty-five patients underwent determination of simultaneous immune bone marrow and serum acid phosphatase before any treatment. While positive values did predict a risk for initial and s ubsequent metastasis, they could not be used to dictate against definitive therapy. Positive bone marrow values were paralleled by positive serum values and provided no additional staging information. (Author abstract) (13 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

6. THE ROLE OF ESTROGEN RECEPTOR STATUS IN PREDICTING THE RESPONSE OF CARCINOMA OF THE BREAST TO ADJUVANT CHEMOTHERAPY.

Stephens RB, Abeloff MD, Mellits ED, Baker RR
Dept. Surgery, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD
Surg Gynecol Obstet; 154(2):200-204 1982

This study was undertaken to determine if there was any correlation between the estrogen receptor status and the response of patients with operable carcinoma of the breast to adjuvant chemotherapy. Seventy-seven patients with metastases to the axillary lymph nodes who were receiving adjuvant chemotherapy following a modified radical mastectomy were studied. During the period of study, 12 of 34 estrogen receptor-positive tumors recurred, with a mean disease-free interval of 17.8 mo, and 19 of 43 estrogen receptor-negative tumors recurred, with a disease-free interval of 15.2 mo. Statistical analysis of recurrence at 2 yr showed no difference between these two groups. Only one patient of 18 in the premenopausal group of women with estrogen receptor-positive tumors, however, had a recurrence compared with 11 of 24 patients with estrogen receptor-negative tumors. This difference was highly statistically significant (p greater than 0.0005). We have concluded that the estrogen receptor status is not a reliable indicator of response to adjuvant chemotherapy for all patients. Our data do indicate a positive correlation between response to adjuvant chemotherapy and estrogen receptor status in the premenopausal group of patients and suggest that adjuvant chemotherapy in the premenopausal group of patients may be exerting some of its effect by ovarian suppression rather than by a solely cytotoxic effect on cancer cells of the breast. (Author abstract) (8 Refs)

7. ESTROGEN RECEPTOR, A MARKER FOR HUMAN BREAST CANCER DIFFERENTIATION AND PATIENT PROGNOSIS.

Osborne CK, Fisher E, Redmond C, Knight WA, Yochmowitz MG, McGuire WL
Dept. Medicine, Univ. Texas Health Science Center, San Antonio, TX, 78284
Adv Exp Med Biol; 138:377-385 1982

Results in a group of patients undergoing mastectomy for primary breast cancer demonstrated that estrogen receptor (ER) may be a biochemical marker for tumor differentiation and is an important independent prognostic variable in such patients. Tumor differentiation and patient prognosis as functions of morphology, correlation of ER with nuclear and histologic grade, with tumor necrosis, elastica, and lymphocyte infiltration, and with prognostically unfavorable morphological characteristics are presented. Implications for therapy of primary breast cancer are discussed. (18 Refs)

8. STEROID RECEPTOR PROTEINS IN HUMAN MENINGIOMAS.

Tilzer LL, Plapp FV, Evans JP, Stone D, Alward K
Clinical Lab., Kansas Univ. Medical Center, Coll. Health Sciences and Hosp., 39th and Rainbow Blvd., Kansas City, KS, 66103
Cancer; 49(4):633-636 1982

Steroid receptor assays play an important role in determining the efficiency of endocrine therapy for patients with breast cancer. Other tumors could also be hormonally dependent and patients with these tumors might also benefit from endocrine manipulation. Thus, patients with meningiomas were tested for the presence or absence of estrogen and progesterone receptors. The results showed that a majority of meningiomas lacked estrogen receptors but contained large amounts of progesterone receptor. Therefore, it should be possible to use antiprogestin therapy in cases where complete surgical resection of meningiomas is not possible. (Author abstract) (10 Refs)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

9. IMMUNO-HISTOLOGICAL ANALYSIS OF BONE MARROW INVOLVEMENT IN LYMPHOPROLIFERATIVE DISORDERS.

Pizzolo G, Chilosi M, Cetto GL, Fiore-Donati L, Janossy G
Sezione di Enatologia, Policlinico di Borgo Roma, 37134 Verona VR, Italy
Br J Haematol; 50(1):95-100 1982

Cryostat sections from bone marrow biopsies submerged in gum-sucrose solution and snap-frozen can be stained with various antisera to detect both the membrane and cytoplasmic antigens on normal and malignant populations in their tissue environments. This technique seems to be the method of choice to analyze the degree of BM involvement in cases of non-Hodgkin's lymphoma where conventional histology provides equivocal results. The uniform expression of only one type of light chain in B lymphoma and the analysis of the T cell infiltrate in T-CLL using monoclonal antibodies is demonstrated. (Author abstract) (9 Refs)

10. UNUSUAL INTRACYTOPLASMIC IMMUNOGLOBULIN INCLUSIONS IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

Guglielmi P, Preud'Homme JL, Gourdin MF, Reyes F, Daniel MT
INSERM U 108, Hopital Saint Louis, 75475 Paris Cedex 10, France
Br J Haematol; 50(1):123-134 1982

Unusual intracytoplasmic immunoglobulin inclusions were found by immunofluorescence in three patients with chronic lymphocytic leukemia. The inclusions contained the same immunoglobulin chains as those detected on the plasma membrane, except for delta chains which were expressed on the cell surface and not in the cytoplasmic inclusions. The cytoplasmic staining persisted throughout culture for 8 or more days. An initial study of patient number one's cells showed that the inclusions contained only mu chains, and kappa chains gradually became apparent after in vitro culture. In a second study, the fresh l ymphocytes contained both mu and kappa chains. Initially, biosynthetic experiments showed production of mu chains which polymerized in the cytoplasm and were not secreted. Subsequently there was synthesis of heavy and light chains which assembled into monomeric subunits that were retained and secretion of free light chains. The apparent mol wt of these immunoglobulin chains was larger than that of their secretory counterparts. Immunoelectronmicroscopy revealed cytoplasmic mu chains in strands of endoplasmic reticulum. In the two other patients, immunofluorescence displayed unusual staining patterns of bright networks in perinuclear areas. (Author abstract) (31 Refs)

11. IMMUNOLOGICAL SUBSETS IN HUMAN B-CELL LYMPHOMAS.

Godal T, Lindmo T, Marton PF, Landaas TO, Langholm R, Hoie J, Abrahamsen AF
Lab. Immunology, Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Scand J Immunol; 14(5):481-492 1981

Fifty human B-cell lymphomas have been studied with regard to surface markers (surface immunoglobulins (sIg) and complement receptors (CR)), capping of sIg, and relative amounts of sIg by single-cell flow cytometry. The results show that these lymphomas can be subdivided into distinct immunological subsets. Whereas one histological subgroup (lymphocytic) consisted of only one immunological subtype, others were heterogeneous with regard to immunological subtypes. This was most striking in nodular lymphomas of germinal center cell origin (centroblastic/centrocytic). Our studies provide further evidence for the existence of a large number of subsets in the B-cell compartment of the immune system. sIgD was only found in association with sIgM. The relative amounts of sIgD varied, especially in nodular lymphomas. A discrepancy between capping of sIgM and sIgD was also found in some lymphomas belonging to this group. These findings together with other observations suggest that sIgD plays a role in B-cell maturation and differentiation events taking place in germinal centers and becomes lost during this process. A close association was found between the presence of CR and capping of sIgM but not capping of sIgD or sIgG. Nodular lymphomas expressing sIgG only, lacked CR. These findings suggest that CR may become lost during maturation and differentiation processes also taking place in germinal centers. Lymphoplasmacytoid lymphomas, which show morphological evidence of differentiation towards plasma cells, could be subdivided into three immunological subsets, indicating that plasma cell maturation may take place from different subsets of B cells. (Author abstract) (39 Refs)

12. T-CELL FUNCTION IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

Whelan CA, Willoughby R, McCann SR
Dept. Immunology, Central Pathology Lab., St. James's Hosp., Dublin 8, Ireland
Br J Haematol; 50(1):111-121 1982

Fifteen patients with chronic lymphocytic leukemia (CLL) were studied. The diagnosis was made by a combination of clinical findings, peripheral blood morphology and cell surface markers. The Rai clinical staging was used to classify all patients. Serum immunoglobulins, B and T cell lymphocytes, TG and TM cell populations were evaluated in all patients before commencing treatment. No correlation was found between clinical staging and the presence or absence of hypogammaglobulinemia. The ratios of TG to TM cells were abnormal in all patients and this abnormality paralleled the stage of the disease. While there was a significant difference in the proliferative responses of highly purified T cell from patients and controls at 1 ug and 2 ug/ml of Concanavalin A (Con A) (p values = p less than 0.005 and p less than 0.01 respectively). There was no significant difference at dose 5 ug/ml. (Author abstract) (37 Refs)

13. HUMAN T-CELL MALIGNANCIES: CORRELATIVE CLINICAL, HISTOPATHOLOGIC, IMMUNOLOGIC, AND CYTOCHEMICAL ANALYSIS OF 23 CASES.

Knowles DM, Halper JP
Coll. Physicians and Surgeons, Lab. Surgical Pathology, Columbia Univ., 630 West 168th St., New York, NY, 10032
Am J Pathol; 106(2):187-203 1982

Twenty-three T-cell neoplasms were investigated for their reactivity with the OKT monoclonal antibodies and expression of certain cytochemical markers. Fourteen neoplasms with diverse histopathologic features, T-cell chronic lymphocytic leukemia, mycosis fungoides, the Sezary syndrome, T-immunoblastic sarcoma, and a pleomorphic large-cell lymphoma, expressed the T helper cell phenotype, OKT3+T4+. Nine other neoplasms displayed marked inter- and intra-tumor heterogeneity. Seven of these cases, lymphoblastic lymphoma, T-cell acute lymphoblastic leukemia, and tumors with features of T-immunoblastic sarcoma or the multilobated lymphoma of Pinkus, expressed intrathymic phenotypes. The other two cases, a lymphoblastic lymphoma and a so-called Lennert's lymphoma, expressed the previously undescribed OKT3+T10+ phenotype. These studies demonstrate that the T-cell malignancies are divisible into phenotypes corresponding to normal maturational stages of T-cell differentiation and functionally distinct T-cell subsets. Such studies should provide a basis for understanding the biologic heterogeneity, clinical diversity, and significance of the variable cytomorphologic characteristics of T-cell malignant tumors and assist in the further delineation of normal human T-cell heterogeneity. (Author abstract) (57 Refs)

14. CHARACTERIZATION OF NORMAL AND MALIGNANT HUMAN LYMPHOID CELL POPULATIONS.

Ford RJ
Dept. Pathology, Univ. Texas M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(6):255-260 1981

Characterization of human lymphoid cell populations with both conventional cell membrane markers and monoclonal antibodies is reviewed. The most reliable human T-cell marker

is the sheep red blood cell rosette assay, usually performed with neuraminidase-treated sheep RBC. The cell-surface immunoglobulin receptor is the most reliable human B-cell marker; others include the membrane receptor for Epstein-Barr virus and the mouse RBC membrane receptor. Monocytes and macrophages may be identified and separated by means of the phagocytosis of latex particles; in addition, enzymes such as alpha-naphthylacetate esterase are relatively specific for the monocyte/macrophage system when present in a diffuse cytoplasmic staining pattern. Hybridoma technology has given rise to the use of mouse monoclonal antibodies for identifying various types of human lymphocytes. Panels of monoclonal antibodies with defined specificities will probably make conventional cell markers obsolete in the near future. Conventional immunologic markers for a number of neoplastic lymphoid cells, including T- and B-cell lymphomas and leukemias and histiocytic lymphomas, are discussed. Recent studies concerning the use of monoclonal antibodies for differentiation of lymphoma and lymphocytic leukemia subtypes are described. (38 Refs)

15. IMMUNOLOGICAL DIAGNOSIS OF VARIANTS OF CHRONIC LYMPHOID LEUKEMIA AND LYMPHOSARCOMA.

Samoilova RS, Ol'shevskaia EV, Polianskaia AM
Lab. Bone Marrow Culturing and Transplantation, Central Inst. Hematology and Blood Transfusion, Moscow, USSR
Ter Arkh; 53(11):73-78 1981

Diagnostic efficacy of determination of surface immunoglobulins (Ig) was studied in 79 patients with various lymphoproliferative diseases. Surface Ig were studied by direct immunofluorescence assay using conjugated gamma-globulin heterosera against heavy and light chains. FC- and CR2-receptors were studied by indirect rosette-formation assay. On the basis of immunologic phenotyping, the lymphoproliferative diseases were divided into B- and T-cell neoplasms. Analysis of surface markers allowed differential diagnosis within the B-cell and T-cell types of neoplasms. Of 48 patients with chronic lymphoid leukemia (CLL), 46 had B-cell variant. Characteristic features of B-cell variant of CLL consisted of low density of surface Ig, presence of CR2-receptor in 44.5% of the cells, presence of Fc-receptor in 17.1% of the cells, and presence of receptor for mouse RBC in 50.4% of the cells. The B-cell variant of prolymphocytic CLL (1 patient) was characterized by high density of surface Ig, low density of CR2-receptor, and extremely low density or complete absence of receptors for mouse RBC. Hairy cell variant of B-CLL (7 patients) was characterized by the absence of CR2-receptors, presence of Fc-receptor, and low density of receptors for mouse RBC. B-cell lymphosarcomas (20 patients) had surface markers similar to those in CLL. T-cell neoplasms (2 CLL, 2 lymphoblastic lymphosarcomas, and 1 acute lymphoblastic leukemia) showed high densities of receptors for sheep RBC. (21 Refs) (In RUS)

16. SPONTANEOUS MOUSE ERYTHROCYTE-ROSETTE FORMATION IN CHRONIC LYMPHOCYTIC LEUKAEMIA.

Kuhlein E, Laurent G, Rigal F, Delsol G, Pris J, Ducos J
Service d'Immunologie, CHU Purpan, 31052 Toulouse Cedex, France
Clin Exp Immunol; 47(2):389-395 1982

Mouse erythrocyte-rosette-forming cells (MRFC) were determined in 76 cases of chronic lymphocytic leukemia (CLL), 19 cases of centroblastic-centrocytic follicular non-Hodgkin's lymphoma (NHL), 5 cases of hairy cell leukemia (HCL) and in 62 control patients. The mean percentage of MRFC in B-CLL was 54.8% +-24.4%, in nodular centro-follicular NHL 2.3% +-3% in hairy cell leukemia 14.6% +-14.7% and among the controls 3.2% +-1.9%. Thus, MRFC appear to be an excellent marker of B-CLL and sometimes the only B cell marker as in 11 cases of SIg negative CLL. There is no correlation between the percentage of MRFC and clinical staging according to Rai classification whereas patients with Stage 2 in Binet's classification (isolated splenomegaly) have a significantly lower MRFC percentage (23.4% +-27.7%, p less than 0.05). There is no correlation with prognosis, nor with serum Ig levels. We found no correlation with surface phenotype IgM, IgM-IgD or IgG. Thus, this study does not confirm the hypothesis that MRFC might characterize an immature stage in the B lymphocyte differentiation. However, these results are consistent with another hypothesis which states that lymphocytes in CLL possibly originate from a clonal expansion of a normal B lymphocyte subset, characterized by a low concentration of SIg and a receptor for mouse erythrocytes. (Author abstract) (26 Refs)

17. ATYPICAL T LYMPHOPROLIFERATIVE DISORDER DEMONSTRATING IN VITRO SUPPRESSOR AND HELPER CHARACTERISTICS.

Proctor SJ, McGregor AM, Clark J, McLachlan S, Dickinson A
Dept. Hematology, Royal Victoria Infirmary, Newcastle upon Tyne, England
Br J Haematol; 50(2):231-240 1982

A patient initially diagnosed on surface marker status as having T cell chronic lymphatic leukemia (T-CLL) was found to have arthropathy and recurrent pulmonary infarction associated with a high anti-DNA antibody titer. The T cells from this patient, on assessment in an in vitro pokeweed mitogen driven B cell system, demonstrated suppressor and helper characteristics but lacked antibody dependent cellular cytotoxicity (ADCC) activity and natural killer (NK) activity. Using peripheral blood mononuclear cells (PBM) from patients with Hashimoto's thyroiditis and normals, it was shown that the patient's T cells suppressed both IgG and thyroid autoantibody production. Irradiation of the patient's PBM inhibited the suppressor effect and a residual helper effect remained. The patient was treated with systemic steroids for exacerbations of arthropathy which caused a fall in lymphocyte count. After 36 mo the DNA binding activity spontaneously improved and the lymphocytosis disappeared. It is indicated that T-cell proliferations demonstrating functional activity must be assessed within the context of any underlying non-hematological clinical and laboratory findings. (Author abstract) (19 Refs)

18. INFLUENCE OF SPLENECTOMY UPON IMMUNOLOGIC REACTIVITY OF PATIENTS WITH HODGKIN'S DISEASE.

Rogan-Grgas J, Milas L, Hauptmann E, Nola P, Kolaric K, Maricic Z, Malenica B
Central Inst. for Tumors and Allied Diseases, 41000 Zagreb, Ilica 197, Yugoslavia
Tumori; 67(6):539-547 1981

Since most patients with Hodgkin's disease benefit from splenectomy, a study was designed to explore whether these beneficial effects could be attributed to the recovery of patients' immunologic reactivity. Using a series of ordinary skin test (PPD-tuberculine, Varidase and Candidin) determination of absolute T and B lymphocyte counts in peripheral blood and their mitogenic responsiveness, assessment of immunologic reactivity was performed in 28 Hodgkin's disease patients, prior to and 14 days after splenectomy. The results showed that

overall immunologic reactivity of these patients was suppressed as judged by low absolute lymphocyte counts (1,747.2 +-171.9), lower counts of T (592.0 +-92.1) and B cells (295.9 +-40.5) and their poor capacity to respond to phytohemagglutinin (PHA) (20,342.6 +-3,662.8 cmp), although the reactivity towards skin test antigens seemed to be well preserved. After splenectomy the reactivity improved, absolute lymphocyte counts raised to 2,654.9 +-468.8 and were parallelled by an increase in T (936.7 +-138.0) and B cell counts (402.2 +-81.2). PHA reactivity recovered as well (26,965.5 +-4,035.6 cpm), however, its remained lower than in control cultures. Furthermore, the immunocompetence of patients' spleens was assessed. The possible influence of some suppressive mechanisms such as serum-blocking factor and prostaglandins is discussed. (Author abstract) (45 Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

19. EARLY JUDGMENT ON THE RESULTS IN RADIATION THERAPY OF COLORECTAL CANCER: DETERMINATION OF CARCINOEMBRYONIC ANTIGEN (CEA) IN BLOOD SERUM AT DAILY INTERVALS FROM THE BEGINNING OF IRRADIATION.

Pompecki R, Schleusner V, Ziegler HW, Winkler R, Rehpenning W
II. Med. Klinik, UK Eppendorf, Martinistrasse 52, D-2000 Hamburg 20, W. Germany
Strahlentherapie; 157(2):81-85 1981

Carcinoembryonic antigen (CEA) and lactate dehydrogenase (LDH) as tumor cell markers have been determined in the blood serum of 10 patients with colorectal cancer, who underwent preoperative irradiation with 200 to 250 rad daily (total focal dose 2,000 to 2,500 rad). Daily analysis was made during the irradiation, and, moreover, a determination 2 wk after the resection of the tumor. Simultaneously CEA and LDH were determined in 10 controls. Serum CEA and LDH levels were found significantly increased in tumor patients as compared to controls. The course was characterized by a peak of LDH on days 4 and 7 from the onset of radiation treatment, while serum CEA did not show a peak in the total of the tumor patients; but in three individual patients a peak was detected. In five patients, with low CEA values from the beginning, no significant modifications of CEA did appear. Thus, some of the patients undergoing irradiation revealed CEA kinetics conform to theoretical considerations, suggesting a response to irradiation of the colorectal carcinoma. The prognostic value of the early CEA kinetics during radiation treatment should be examined in patients being irradiated for inoperable local recurrence. (Author abstract) (16 Refs) (In GER)

20. ON DIAGNOSTIC VALUE OF DETERMINATIONS OF CHORIONIC GONADOTROPIN AND TROPHOBLASTIC BETA1-GLYCOPROTEIN IN TROPHOBLASTIC DISEASE.

Grinevich IuA, Tatarinov IuS, Iugrinova LG, Olefirenko GA, Dotsenko IuS
Res. Inst. Roentgeno-Radiology and Oncology, Kiev, USSR
Vopr Onkol; 27(12):19-23 1981

The diagnostic value of determinations of the levels of chorionic gonadotropin (HCG) and trophoblastic beta1-glycoprotein (TBG) was studied in 160 cases of trophoblastic disease. Trophoblastic disease was diagnosed in 86% of cases, when HCG level was determined immunologically and in 100% - by radioimmunological means and in 86 and 33%, when TBG level was established by immunoradioautographical and immunodiffusion methods, respectively. The results of HCG and TBG assays by immunological and immunoradioautographical methods matches in 96% of cases. The said methods are highly specific and may find a wide application in diagnosing trophoblastic disease. The radioimmunological method of HCG assay is the most sensitive. However, in view of possible HCG synthesis in cases of other tumor, its application should be preferred in assessing the efficacy of therapy rather than for primary diagnosis of trophoblastic disease. (Author abstract) (8 Refs) (In RUS)

21. PLACENTAL PROTEINS (SP1, HCG, PP5), AND ALPHA2-PAG IN TROPHOBLASTIC DISEASES.

Than GN, Bohn H, Csaba IF, Szabo DG, Karg NJ, Gocze P
(c/o Csaba) Dept. Obstetrics and Gynecology, Univ. Medical Sch., Edesanyak utja 17, P.O. Box 89, H-7624 Pecs, Hungary
Arch Gynecol; 231(1):33-39 1981

Monitoring system for patients with trophoblastic tumor is discussed. Pregnancy-specific beta-1glycoproterin (SP1), pregnancy-associated alpha-2 glycoprotein (alpha2-PAG), beta subunit of human chorionic gonadotropin (hCG), and the placental protein 5 (PP5) soluble protein specific for placental tissue are regularly monitored in patients. A total of 455 serial serum samples from 41 patients with trophoblastic tumor (26 hydatidiform mole, 8 chorioadenoma, 7 choriocarcinoma) were analyzed. SP1, hCG, and PP5 were measured by the specific radioimmunoassay. Alpha2-PAG was measured by electroimmunoassay. Sp1 levels were high in 36 patients, hCG levels in 35 patients, and alpha2-PAG levels in 29 patients. PP5 was found only in patients with a hydatidiform mole and disappeared from sera within a few hr after evacuation. SP1 and hCG levels decreased during treatment but seronegativity was reached only after some mo. hCG disappeared from serum more slowly. In some patients only one of the tumor markers was present during follow-up. Careful monitoring including measurements of serum SP1 and hCG levels is important. Positive correlation between alpha2-PAG, hCG, SP1 and clinical course was found in only 80% of patients. Case reports of a 42-yr-old patient with uterine choriocarcinoma treated by hysterectomy and chemotherapy, and of a 41-yr-old patient treated for choriocarcinoma which developed shortly after a hydatidiform mole, are presented. (21 Refs)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

22. SERUM FERRITIN AND BINDING OF SERUM FERRITIN TO CONCANAVALIN A AS A TUMOR MARKER IN PATIENTS WITH PRIMARY LIVER CELL CANCER AND CHRONIC LIVER DISEASE.

Chapman RW, Bassendine MF, Laulicht M, Gorman A, Thomas HC, Sherlock S, Hoffbrand AV
Dept. Medicine, MRCP, Pond St., London, NW3 2QG, England
Dig Dis Sci; 27(2):111-116 1982

Total ferritin concentration was measured in sera of 30 patients with primary liver cell cancer (PLCC) and 33 patients with cirrhosis and compared with serum alpha-fetoprotein levels as a diagnostic marker of PLCC. Serum ferritin concentration was raised in 19 patients (63%) with PLCC and 11 pa-

tients (33%) with cirrhosis. The median level was significantly higher (p less than 0.001) in the PLCC group (560 ug/liter) than in the cirrhotic group (137 ug/liter), although there was considerable overlap. Serum ferritin was positively correlated with serum aminotransferase levels in the cirrhotic patients (r = 0.53, p less than 0.001), reflecting hepatic necrosis, but not in the PLCC patients. The concentration of ferritin binding to concanavalin A was measured in the sera of patients with elevated total serum ferritin. Although the proportion of bound ferritin was decreased in the majority of PLCC sera compared to controls (p less than 0.001), there was overlap with the cirrhotic group, making it unlikely that this assay is useful in distinguishing a tumor-specific isoferritin. Serum alpha-fetoprotein levels were elevated in 21 patients (70%) with PLCC and proved to be a highly sensitive and specific test for PLCC. There was no relationship between the alpha-fetoprotein and serum ferritin concentrations. Serum ferritin is inferior to alpha-fetoprotein as an initial screening test for PLCC, but in alpha-fetoprotein-negative patients serum ferritin may have a role in monitoring therapy. Patients with cirrhosis with normal serum alpha-fetoprotein and ferritin concentrations are very unlikely to have PLCC. (Author abstract) (20 Refs)

23. DETERMINATION OF URINARY MELANOGEN IN 40 CASES OF MALIGNANT MELANOMA.

Bucciarelli M, Bertazzoni MG, Motolese A
Clinica Dermosifilopatica, Universita di Modena, Modena, Italy
Chron Dermatol; 12(3):375-379 1981

Urinary melanogen was determined in 40 patients with malignant melanoma (MM) and in 12 controls (patients with other diseases), using Thormahlen's test. The results of the test were always negative (amber color) in the controls. Of the 20 MM patients without clinical evidence of metastases, the results of the test were negative in 17 and slightly positive in 3 (pale green color). Of the six MM patients with lymph nodes or skin metastases surrounding the lesion, the results of the test were negative in one and slightly positive in five. Of the 14 MM patients with visceral metastases, the results of the test were negative in 1 case, positive in 7 (intense green color) and strongly positive in 6 (blue-green color). When the test was repeated later on in 14 cases, the results remained unchanged in 10 patients who did not show clinical change; however, in 4 patients who previously had negative or slightly positive results, the color changed, indicating more positive results following the appearance of metastases. The test was useful in prognosis of MM. (15 Refs) (In ITA)

24. PROTEINS OF HUMAN URINE. II. IDENTIFICATION BY TWO-DIMENSIONAL ELECTROPHORESIS OF A NEW CANDIDATE MARKER FOR PROSTATIC CANCER.

Edwards JJ, Anderson NG, Tollaksen SL, Von Eschenbach AC, Guevara J
Molecular Anatomy Program, Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, Il, 60439
Clin Chem; 28(1):160-163 1982

A protein series common to the urine and prostatic tissue of 16 of 17 patients with prostatic adenocarcinoma has been identified by high-resolution two-dimensional gel electrophoresis. These proteins, designated PCA-1, have a relative molecular mass in sodium dodecyl sulfate of about 40,000. Analyses of urines from eight age-matched controls, seven patients with other types of urogenital malignancies, two patients with benign prostatic hyperplasia, and five patients with malignancies not associated with the urogenital system failed to show PCA-1 in the patterns. These preliminary findings suggest that this protein should be systematically investigated as a candidate marker for prostatic adenocarcinoma in man. (Author abstract) (23 Refs)

25. CONCENTRATION OF NEURAMINIC ACID IN THE SERUM OF TUMOR PATIENTS.

Prignitz R, Rainer K, Biller H, Prignitz I
Klinik und Poliklinik fur Strahlentherapie und Rontgendiagnostik, Robert-Koch-Strasse 8n, D-3550 Marburg, W. Germany
Strahlentherapie; 157(1):37-40 1981

The neuraminic acid level in the serum of 588 patients was determined. The patients suffered from bronchial carcinomas, other malignant diseases (mastocarcinoma, carcinoma of the cervix and the body of the uterus, Hodgkin's lymphoma, non-Hodgkin's lymphoma), and benign pulmonary diseases (tuberculosis of the lungs and chronic obstructive pulmonary diseases). The av level of 162 patients with bronchial carcinomas is 3,449 umol/ml of serum; thus it is significantly higher than the av level of 98 sound control persons (2,336 umol/ml) and 88 patients with benign pulmonary diseases (2,733 umol/ml). The other patients with malignant diseases also presented an increased concentration of neuraminic acid in the serum, however, this increase was not as significant as for the patients with bronchial carcinomas. The possible role of neuraminic acid as a biological 'marker' is discussed. (Author abstract) (30 Refs) (In GER)

26. NEOPTERIN EXCRETION IN URINE IN PATIENTS WITH GYNECOLOGICAL TUMORS.

Hetzel H, Bichler A, Fuchs D, Hausen A, Konig K, Wachter H
Universitatsklinik fur Frauenheilkunde, Anichstrasse 35, A-6020 Innsbruck, Austria
Gynaekol Rundsch; 21(Suppl2):218-220 1981

Neopterin excretion (NPE) was measured in 317 urine samples from patients with gynecological tumors as well as from healthy male and female patients. Patients with genital carcinomas showed significantly higher NPE than healthy controls. NPE values coincided with diagnosis of carcinoma in 62% of cases. In monitoring the course of disease NPE values corresponded to radiological findings in 76% of cases. (3 Refs) (In GER)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

27. ENZYMES OF NORMAL, PREMALIGNANT, AND MALIGNANT COLONIC CELLS.

Balis ME, Higgins PJ, Salser JS, Stemmerman GN, Magee PN, Wattenberg LW
Dept. Cell Metabolism and Cell Biochemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Banbury Rep; 7:129-139 1981

The villus and crypt cells of rat small intestine contained two different forms of adenosine deaminase (AD) and adenine phosphoribosyltransferase (APRT). The APRTs of normal and neoplastic rat colonic mucosa showed similar properties. Normal colonic mucosa showed predominantly one form of AD, but colonic tumors induced by methylazoxymethanol showed two distinct forms. The ADs of human colonic mucosa and colonic cancer were also distinctive. The tumor AD was

smaller than that of normal tissue and was also immunologically distinct. In rat colon, ornithine decarboxylase (ODC) activity was about the same as in liver and only 1-2% that of the small intestine. Carcinogens caused a marked increase in the ODC activity of the target tissue: acetylaminofluorene in the liver, and dimethylhydrazine (DMH) in the colon. Thymidine kinase (TK) activity of the intestine was much higher in the fetal rat than in young or mature rats. After the administration of a colonic carcinogen (DMH), the colonic TK activity increased to levels resembling the fetal TK activity. Assays using rabbit antisera demonstrated two types of TK in normal human intestine, representing the flat mucosa and the crypts. A rabbit antibody against TK from human term placenta cross-reacted against cells from a number of tumor types, including abnormal cervical cells in Papanicolaou smears and colon carcinoma cells. This antibody also reacted with skin fibroblasts from patients with familial colonic polyposis. The specificity of the TK antibody for a variety of tumor types was greatly reduced by preabsorbing the rabbit antiserum with normal human colon extracts. (11 Refs)

28. CONCOMITANT INDUCTION OF THE CELL SURFACE EXPRESSION OF IA DETERMINANTS AND ACCESSORY CELL FUNCTION BY A MURINE MACROPHAGE TUMOR CELL LINE.

Walker EB, Lanier LL, Warner NL
Immunology Lab., Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131
J Exp Med; 155(2):629-634 1982

The induction of cell surface Ia molecules on an Ia-negative, murine macrophage tumor, WEHI-3, and the subsequent ability of this Ia-induced tumor lines to provide accessory cell function in a major histocompatibility complex-restricted, antigen-driven, in vitro assay system are described. Uncharacterized soluble factor produced in concanavalin A-induced rat spleen cell suspensions had the capacity to induce the increased expression of cell surface H-2K and H-2D molecules and the expression of I-region gene products on murine monocyte-macrophage lineage tumors that were not Ia positive in the absence of the factor. (10 Refs)

29. EPSTEIN-BARR VIRUS SUSCEPTIBILITY OF B CELLS CORRELATES TO THE PRESENCE OF COMPLEMENT RECEPTORS BUT NOT SURFACE IMMUNOGLOBULINS.

Takada K, Osato T
(c/o Osato) Dept. Virology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo 060, Japan
Intervirology; 16(2):118-122 1981

Nuclear antigen (EBNA) inducibility by Epstein-Barr virus (EBV) was assessed in relation to the presence of complement (C3) receptors and surface immunoglobulins (SIg) on leukemic lymphocytes. When erythrocyte-antibody-complement complex (EAC)-positive, SIg-negative B cells were exposed to EBV, EBNA synthesis occurred with a high frequency. In contrast, no significant EBNA induction was evident in SIg-positive, EAC-negative B cells. Cells possessing both markers were EBV-infectable, in proportion to the frequency of EAC-rosette formation. These data seem to indicate that EBV susceptibility of human B cells is closely related to the presence of C3 receptors but not SIg. Leukemic T cells an d myelogenous leukemia cells were not EBV-susceptible, although some cells were significantly positive for C3 receptors. (Author abstract) (15 Refs)

30. CHARACTERIZATION AND FUNCTIONAL PROPERTIES OF TUMOR CELL LINES IN ACCESSORY CELL REPLACEMENT ASSAYS.

Walker EB, Lanier LL, Warner NL
Immunobiology Lab., Dept. Pathology and Medicine, Univ. New Mexico Sch. Medicine, 2701 Frontier NE, Surge Building, Albuquerque, NM, 87131
J Immunol; 128(2):852-859 1982

This study reports the initial phenotypic and functional characterization of a series of cloned, murine, myelomonocytic tumors and their parent cell line WEHI-3, and a group of murine B lymphoma tumors. The tumor cell lines of the myelomonocytic lineage demonstrated the ability to reconstitute a macrophage-depleted, primary in vitro anti-SRBC PFC response, but only marginally enhanced an accessory cell-depleted, ova-primed, lymphocyte proliferation in vitro response. The B lymphoma tumors displayed exactly the reverse functional profile, being highly efficient in reconstitution of the proliferation response, but not supporting the SRBC PFC response. Detailed analysis of the cell surface phenotype of the various B lymphoma tumors used in this study show they display cell surface markers characteristic of normal B lymphocytes but are heterogeneous in their various stages of differential arrest. Future work will concentrate on the orchestration of Ia-mediated and soluble factor-mediated (IL 1) modalities of antigen-triggering of lymphocytes by these B lymphoma and myelomonocytic tumor cell lines. (Author abstract) (46 Refs)

31. B LYMPHOBLAST ANTIGEN (BB-1) EXPRESSED ON EPSTEIN-BARR VIRUS-ACTIVATED B CELL BLASTS, B LYMPHOBLASTOID CELL LINES, AND BURKITT'S LYMPHOMAS.

Yokochi T, Holly RD, Clark EA
(c/o Clark) Regional Primate Res. Center and Dept. Genetics, Univ. Washington, Seattle, WA, 98195
J Immunol; 128(2):823-827 1982

Two new cell surface antigens expressed on B lymphoblastoid cell lines (B-LCL) were defined with cytotoxic mouse monoclonal antibodies. One marker, BB-1 (for B lymphoblast antigen-1), was detected on human and nonhuman primate B-LCL, Epstein-Barr virus (EBV)-activated B cell blasts, most Burkitt's lymphomas, and Ia+ B lymphoblast-like myelomas. Polyclonal B cell activators such as pokeweed mitogen (PWM) and lipopolysaccharide (LPS) also induced the expression of BB-1 on immunoglobulin (Ig)-positive cells.In contrast, BB-1 could not be detected on normal lymphoid tissues by complement-dependent cytotoxicity and immunofluorescence (IF) assays or by analysis with a fluorescence-activated cell sorter (FACS). T cell blasts, T cell leukemias, and pre-B cell or erythroblastic leukemia cell lines were also BB-1 negative. Of particular interest was the finding that BB-1 was expressed on the Jijoye lymphoma but only marginally on a subline of Jijoye, P3HR-1, that lacks receptors for EBV and produces a defective virus incapable of transforming lymphocytes. A second lymphoblast antigen (LB-1) unlike BB-1, was present on both T and B cell blasts and virus-transformed T- and B-LCL but not on normal lymphoid tissues. (Author abstract) (50 Refs)

32. EXPRESSION OF RED CELL SPECIFIC DETERMINANTS DURING DIFFERENTIATION IN THE K562 ERYTHROLEUKAEMIA CELL LINE.

Horton MA, Cedar SH, Edwards PA
Dept. Haematology, St. Bartholomew's Hosp., London, EC1A 7BE, England
Scand J Haematol; 27(4):231-240 1981

A human hemopoietic cell line (K562) which exhibits various erythroid characteristics, has been utilized as a model system for studying erythropoietic differentiation. We have analyzed the alterations in expression of cell membrane determinants which accompany the induction of Hb synthesis. We confirm that the K562 cell line exhibits a number of erythroid features: it expresses immunologically detectable membrane proteins, glycophorin A and spectrin, and can be induced, by addition of hemin or n-butyrate, to synthesize Hb. N and i-like blood group activities are demonstrable in uninduced K562, but band 3, ABH and other major alloantigens characteristic of mature erythrocytes are lacking. The acquisition of cell surface antigens typifying erythroid or other hemopoietic lineages has not been demonstrated following induction, although certain properties not associated with morphologically recognizable red cell precursors are lost. The relevance of these findings to the fetal nature and possible multipotentiality of the K562 cell line are discussed. (Author abstract) (25 Refs)

33. OT-CLL: A HUMAN T CELL CHRONIC LYMPHOCYTIC LEUKEMIA THAT PRODUCES IL 2 IN HIGH TITER.

Friedman SM, Thompson G, Halper JP, Knowles DM
Div. Rheumatology, Dept. Medicine, Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Immunol; 128(2):935-940 1982

This report identifies and describes a human T cell chronic lymphocytic leukemia, OT-CLL, which can be triggered by selected mitogens (either PHA or Con A) to produce IL 2 in high titer. Optimal IL 2 production requires culturing OT-CLL cells at 2 to 5 x 10(6)/ml for 24 hr in the presence of 1 to 2% PHA-M. Under these conditions, the titer of IL 2 generated is greater than 20-fold that obtained from conventional sources, eg, from mitogen-activated tonsillar lymphocytes. Two lines of experimental evidence suggest that the tumor cell product(s) is IL 2. First, in functional assays, supernatants derived from cultures of PHA-activated OT-CLL cells trigger the proliferation and long-term growth of IL 2-dependent human TCL cells. Second, a partial biochemical purification of the active moiety(ies) derived from OT-CLL demonstrates marked similarity to conventional human IL 2. Thus, the biologically active material(s) precipitates in 50 to 70% saturated (NH4)2SO4 solutions; elutes from DEAE-Sepharose in the presence of 0.04-0.08 M NaCl; and has an apparent mol wt of approx 14,000, as determined by Sephadex G-100 gel filtration. In addition, analysis of OT-CLL cells by indirect immunofluorescence, utilizing a panel of monoclonal antibodies, confirms not only that these tumor cells are of T cell lineage but that they display surface antigens that define the normal human peripheral T cell subset subserving helper or inducer function: OKT3+, OKT4+, OKT8-. (Author abstract) (36 Refs)

34. ELEVATED URINARY EXCRETION OF RNA CATABOLITES AS AN EARLY SIGNAL OF TUMOR DEVELOPMENT IN MICE.

Thomale J, Nass G
Zentrallabor fur Mutagenitatsprufung, Deutschen Forschungsgemeinschaft, Breisacher Str. 33, D-7800 Freiburg, W. Germany
Cancer Lett; 15(2):149-159 1982

Urinary excretion rates of 12 modified nucleosides and bases were determined in male C57Bl/6J mice with 3-methylcholanthrene (MCA: 100 ug, sc)-induced tumors. Excretion of the RNA catabolites started to increase 7 wk after tumor induction. Mice with advanced tumors showed significantly higher excretion rates than untreated controls. Some metabolites, including 7-methylguanine (m7Gua), N2-methylguanine (m2Gua), 1-methyladenosine, N4-acetylcytidine, 5-methylcytidine, and 5-(beta-D-ribofuranosyl)uracil, showed distinct increases in urinary excretion before wk 16, the earliest point at which tumors could be detected. m7Gua and m2Gua were very sensitive tumor indicators. MCA-treated mice that did not develop tumors excreted normal levels of catabolites, indicating that the methyl groups of those catabolites were not derived from the carcinogen. Increased nucleoside and base excretion in tumor-bearing animals is apparently an expression of altered overall metabolism. (16 Refs)

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. THE PROTOCOL FOR LONG-TERM FOLLOW-UP OF TREATED OVARIAN CANCERS. COELIOSCOPY AND CARCINO-EMBRYONIC ANTIGEN ASSAY.

Bernard P, Kac D, Boury-Heyler, Rochet Y
Service de Gynecologie, Pavillon Paul-Gerin, CHU de Grenoble, BP 217 X, F 38043 Grenoble, France
Gynecologie; 32(4/5):379-384 1981

Coelioscopy is recommended as an excellent follow-up method for patients who underwent treatment for ovarian cancer because it allows a direct vision of the pelvic, digestive, and peritoneal cavities. Areas of peritoneal granulations may be recognized. These granulation areas may then be biopsied, and cytologic examination of cells acquired through peritoneal lavage with physiologic serum may be carried out. Extreme care in the technique used for the examination is recommended because of the high risk of digestive trauma. Coelioscopy is usually carried out 2x a yr but frequency of the examination is in fact dictated by the levels of carcinoembryonic antigen (CEA) should be prescribed for 5 yr following surgery. CEA levels are elevated in 73% of the women who have had ovarian cancer. A level higher than 15 nanog/ml is considered pathologic. The two cases presented demonstrate the importance of close follow-up. In one case, exploratory laparotomy revealed an intraclinical recurrence limited to a single peritoneal metastasis. In the other case. Positive cytology obtained through normal coelioscopic examinations led to further chemotherapy and exploratory laparotomies. (8 Refs) (In FRE)

2. CARCINOEMBRYONIC ANTIGEN IN CASES OF CERVICAL CARCINOMA.

Weppelmann B, Schulz BO, Oberheuser F
Jewish Hosp., Burnett Ave., Cincinnati, OH, 45229
Zentralbl Gynaekol; 103(21):1273-1279 1981

Carcinoembryonic antigen (CEA) was determined by means of solid-phase radioimmunoassay through 1 yr in 83 patients with Groups I through IV cervical carcinoma. The intention was to test CEA diagnosis for its value as a tumor marker in therapeutic monitoring and detection of recurrences. CEA values prior to treatment were above normal, that is in excess of 2.5 ng/ml, in 42.8% of the cervical carcinoma patients. CEA values declined during therapeutic radium and cobalt60 irradiation in 81% of those patients in whom original values had been increased to more than 2.5 ng/ml. No substantive change was recordable from those patients in whom original values had been below 2.5 ng/ml. Recurrence diagnosis gave good agreement between CEA levels and clinical findings in 58% of the cases, falsely negative data in 37% and falsely positive values in 4%. The development of recurrence was repeately sensed by means of CEA determination up to 6 mo before clinical manifestation in 72 patients who had been under long-time monitoring. The usefulness of CEA determination in therapeutic monitoring and after-care of patients with cervical carcinoma was found to be limited to the effect that only increased values were of clinical relevance, whereas no conclusions whatever could be drawn from low values. (Author abstract) (21 Refs) (In GER)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

3. ELEVATED GAMMA-GLUTAMYL TRANSPEPTIDASE LEVELS IN MALIGNANT MELANOMA.

Murray JL, Lerner MP, Nordquist RE
Cancer Res. Program, Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklaho ma City, Oklahoma, 73104
Cancer; 49(7):1435-1443 1982

Serum gamma(glutamyl) transpeptidase (GGTP) levels were measured in 50 patients with malignant melanoma to determine whether the enzyme was a sensitive indicator of disease status. Patients were divided into three groups based on clinical stage. Eighteen patients, following complete surgical resection of their primary disease, had a mean GGTP value of 10.97 International Units/Liter, which was not significantly different from the mean of healthy controls (10.2 +-2.5; range, 5.6-15.2). Likewise, eight patients who had undergone resection of regional disease or solitary metastasis had values near the upper range for controls. Serial testing in 15 of the above patients revealed no significant fluctuations on a daily or monthly basis. In contrast, individuals with metastatic disease has significantly elevated GGTP levels and demonstrated stepwise increases with disease progression. In seven patients enzyme levels were predictive of either recurrent disease or response to therapy. We conclude that serum GGTP levels are a useful test in monitoring clinical status of melanoma patients. (Author abstract) (20 Refs)

4. PLASMA FUCOSYLTRANSFERASE AS AN INDICATOR OF IMMINENT BLASTIC CRISIS.

Shah-Reddy I, Kessel DH, Chou T, Mirchandani I, Khilanani U
Section Hematology, Hutzel Hosp., 4707 St. Antione, Detroit, MI, 48201
Am J Hematol; 12(1):29-37 1982

Plasma fucosyltransferase activity was evaluated as an indicator of an impending blastic transformation in 25 patients with chronic granulocytic leukemia (CGL). Fifteen age- and sex-matched controls were also studied. The level of enzyme activity was significantly higher in the plasma of patients with blastic transformation (1,630 +-570 units) compared with steady state chronic granulocytic leukemia (509 +-110 units) and normal controls (354 +-57 units). In three patients with CGL, a rise in fucosyltransferase activity preceded any other clinical or laboratory parameter of blastic transformation by 16-20 wk. (Author abstract) (22 Refs)

5. SIALYLTRANSFERASE, SIALIC ACID AND SIALOGLYCOCONJUGATES IN METASTATIC TUMOR AND HUMAN LIVER TISSUE.

Alhadeff JA, Holzinger RT
Dept. Neurosciences, Sch. Medicine Univ. California, San Diego, La Jolla, CA, 92093
Int J Biochem; 14(2):119-126 1982

Glycoprotein-sialyltransferase activity (with the use of tritiated substrates) was assayed under optimal conditions in homogenates of metastatic tumor sites, non-cancerous host tissue, and non-pathological control livers. In all of the studies, results for uninvolved host liver tissue were very similar to those of the non-pathological control liver. For each liver, the metastatic tumor site had 3-37% of the sialyltransferase activity of the adjacent uninvolved non-cancerous tissue. The uninvolved non-can cerous tissues had a wide range of sialytransferase ac-

tivities (106-1,836 dpm/min/mg protein) and an av activity (986) slightly lower than the av of non-pathological livers (1,194). The levels of total and bound sialic acid were increased 1.4 to 7.2-fold in homogenates, supernatants and resuspended pellets of metastatic tumor sites compared to non-cancerous and non-pathological control livers. In all these tissues, 24-29% of the bound sialic acid was found on soluble components (in the 16,300 x gravity supernatant). The gel filtration profiles of soluble sialoglycoconjugates from most metastatic tumor sites were different from those of the non-cancerous and non-pathological control livers. (34 Refs)

6. SERUM NEURON-SPECIFIC ENOLASE: A MARKER FOR DISEASE EXTENT AND RESPONSE TO THERAPY OF SMALL-CELL LUNG CANCER.

Carney DN, Ihde DC, Cohen MH, Marangos PJ, Bunn PA, Minna JD, Gazdar AF
Natl. Cancer Inst., Navy Medical Oncology Branch, Natl. Naval Medical Center, NCI, Bethesda, MD, 20205
Lancet; 1(8272):583-585 1982

Serum neuron-specific enolase (NSE) levels in 94 newly diagnosed untreated patients with small-cell lung cancer (SCLC) were compared with those in 30 adult controls. Thirty-eight of the SCLC patients had limited disease and 56 had extensive disease. Serum NSE was raised (greater than 12.0 ng/ml) in 69% of all patients (mean 52.35 +-11.56, range 4.1-850 ng/ml); it was raised in 15/38 (39%) of patients with limited stage disease and in 49/56 (87%) of those with extensive stage disease. Extensive stage patients had a significantly higher mean NSE level (59 ng/ml) than did limited stage patients (13.8 ng/ml). Serum NSE was raised in 34/41 (84%) of patients with metastases at 1 or 2 sites and in all 15 patients with metastases at 3 or more sites. Serial measurements in 23 patients receiving combination chemotherapy showed an excellent correlation between serum NSE and clinical response. Continuous cell-lines of SCLC, established from 10 of the patients in this study, all expressed high levels of NSE. These studies indicate that serum NSE may be a useful marker for staging and for monitoring response to therapy in patients with SCLC. (Author abstract) (25 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

7. EFFECTS OF ENDOCRINE THERAPY ON STEROID-RECEPTOR CONTENT OF BREAST CANCER.

Taylor RE, Powles TJ, Humphreys J, Bettelheim R, Dowsett M, Casey AJ, Neville AM, Coombes RC
(c/o Coombes) Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Br J Cancer; 45(1):80-85 1982

In order to determine the mechanisms of relapse following response to endocrine therapy, we have measured the estrogen receptor (RE) content of biopsies of breast cancer in patients receiving various types of endocrine treatment. RE content fell in responding (means of 260.2 to 12 fmol/mg protein) and in nonresponding (means of 155.1 to 31.8 fmol/mg protein) patients who had measurable receptor at the start of treatment. Some of these patients, and a further group of responders to endocrine therapy, were monitored until relapse. Tumor biopsies at the time of relapse showed that 10/14 tumor samples contained significant RE (mean of 86.7 fmol/mg protein; range less than 10-271 fmol/mg protein) after successful endocrine therapy. No relationship could be found between RE content and plasma gonadotrophin or steroid-hormone concentration, but the fall in RE content correlated with reduced numbers of tumor cells in the biopsy. These results indicate that relapse following successful endocrine therapy in breast cancer does not appear to be due to the emergence of RE-negative tumor cells. The fall in RE content during response to endocrine therapy may be due to reduced tumor-cell content of the biopsy. (Author abstract) (19 Refs)

8. STUDIES ON NUCLEAR ESTRADIOL RECEPTORS IN HUMAN MAMMARY CARCINOMAS.

O'Connell M, McDonnell L, Duffy MJ
(c/o Duffy) Nuclear Medicine Dept., St. Vincent's Hosp., Dublin 4, Ireland
Clin Chim Acta; 119(3):285-289 1982

It is known that 50-70% of human primary mammary carcinomas possess cytoplasmic estradiol receptors (CER) and that over 5x as many CER- as non-CER-carcinomas respond to hormone manipulative therapy. This study demonstrates that 59% of CER- and 24% of non-CER carcinomas possess nuclear estradiol receptors (NER), whose presence should be a better indicator of amenability to this therapy. The correlation between CER and NER is $r = 0.55$ ($p = 0.0001$, $n = 92$). NER does not correlate with tumor cellularity, size, histological type, presence/absence of axillary node metastases, or cytosol levels of either total estrogens or progesterone. Presence or absence of NER does not alter the total cytosol estrogens median or the cytosol progesterone mean level. The percentage of tumors with over 25 fmol NER receptor/g wet weight decreases as the histologic tumor grade or stage increases, but not in a statistically significant manner. The significance of these findings is discussed in relation to recent literature on NER and CER, and rests upon results of ongoing clinical studies. (13 Refs)

9. ESTROGEN SULFURYLATION AS AN ALTERNATIVE INDICATOR OF HORMONE DEPENDENCE IN HUMAN BREAST CANCER.

Pewnim T, Adams JB, Ho KP
Sch. Biochemistry, Univ. New South Wales, Sydney, N.S.W. 2033, Australia
Steroids; 39(1):47-52 1982

Estrogen receptor (ER) levels, formation of 3'-phosphoadenosine-5'phosphosulfate (PAPS), and sulfate transfer to estradiol-17beta, have been determined in 62 human primary carcinoma cytosol preparations. While no differences between ER positive and ER negative tumors were found in the synthesis of [35S]PAPS, formation of estradiol-3-[35S]sulfate catalyzed by estrogen sulfotransferase was significantl y higher in ER positive tumors [84 +-10 (mean +- S.E.M.) vs 32 +-9 pmole estradiol-3-sulfate per mg protein per 2 hr for ER positive and ER negative tumors, respectively, p less than 0.02]. By choosing a discriminating value for estrogen sulfurylation of 40 pmole per mg protein per 2 hr, then 16/19 (84%) of the ER negative tumors were below this point. Since previous data had shown that 20/23 (87%) progesterone receptor negative tumors were also below this value, an alternative simple method, having a high potential for the evaluation of hormone responsiveness in mammary cancer, is suggested. (Author abstract) (7 Refs)

10. NUCLEAR ANDROGEN RECEPTOR AS MARKER OF RESPONSIVENESS TO MEDROXYPROGESTERONE ACETATE IN HUMAN RENAL CELL CARCINOMA.

Concolino G, Marocchi A, Toscano V, Di Silverio F
Istituto di Clinica Medica Generale e Terapia Medica V, Universita di Roma, Roma, Italy
J Steroid Biochem; 15:397-402 1981

Androgen receptors (AR) were measured in the cytoplasmic and nuclear fractions of human renal cell carcinoma (RCC) in order to find a parameter (ARn) which could better predict the response to hormonal therapy. Cytosol AR were detected in 50% and ARn in 57% of the tumors examined. AR do not only help to define the hormone-dependent human RCC, but may also be useful in the selection of patients to be treated with medroxyprogesterone acetate (MPCA). MPCA could counteract the promoting action of estrogens on tumor growth only in patients with ARn positive tumor. (27 Refs)

11. IN VITRO GLUCOCORTICOID STUDIES IN HUMAN LYMPHOMA: CLINICAL AND BIOLOGIC SIGNIFICANCE.

Bloomfield CD, Smith KA, Peterson BA, Gajl-Peczalska KJ, Munck AU
Univ. Minnesota Hospitals, Box 277, Minneapolis, MN, 55455
J Steroid Biochem; 15:275-284 1981

Results from summarized studies of receptor levels from tumor cells from different tissues, in vitro glucocorticoid (GC) assays in control lymph nodes and in lymphoma, in vitro GC assays and response to GC therapy, effect of in vivo GC administration on receptor levels, and sequential studies of tumor receptors at diagnosis and relapse, on patients and volunteers, are presented. Receptor levels in tumor cells from different sites did not correlate well and since sufficient numbers of lymphoma cells (LC) from marrow and blood are available in less than 25% of patients, LC from lymph nodes were used. Median number of GC receptor sites/cell were 691 for cytoplasmic receptors, 1,481 for nodular, and 2,085 for total receptors. Inhibition of leucine incorporation by dexamethasone (DM) was significantly greater in lymphomas than in control lymph nodes. Significant differences between responders and nonresponders were not seen in DM inhibition of radiolabeled leucine or thymidine incorporation. No pretreatment clinical characteristics could be used to predict those patients who would respond to GC therapy. The fall in receptor numbers following GC administration could be explained as intrinsic regulation by the cell of receptors in response to in vivo changes in hormone (GC) level (down regulation). Data suggest that following relapse, cases initially sensitive to GC may develop resistance by selection of cells with fewer receptors, and administration of DM to patients may result in selection of lymphoma cells with lower number of receptors. Chemotherapy in addition to GC may accelerate the process. (27 Refs)

12. THE BIOCHEMICAL PROPERTIES OF URINARY HUMAN CHORIONIC GONADOTROPIN FROM THE PATIENTS WITH TROPHOBLASTIC DISEASES.

Nishimura R, Endo Y, Tanabe K, Ashitaka Y, Tojo S
Dept. Obstetrics and Gynecology, Kobe Univ. Sch. Medicine, Kobe 650, Japan
J Endocrinol Invest; 4(3):349-358 1981

Human chorionic gonadotropin (hCG) was extracted from urine of a 23-yr-old woman with a hydatidiform mole, a 37-yr-old woman with metastatic choriocarcinoma, and a woman with a normal pregnancy by the standard kaolin-acetate method in conjunction with alcohol precipitation. Purification by diethylaminoethyl-cellulose chromatography and Sephadex G-100 gel filtration was followed by determination of amino acids, carbohydrates, and monosaccharides, sodium dodecyl sulfate polyacrylamide gel electrophoresis, 125I-hCG radioimmunoassay, 125I-hCG uptake in rats, and bioassay by ovarian wt method. Amino acid compositions of the three hCG samples were virtually identical. All three types of hCG could be separated into alpha and beta components by electrophoresis. They were similar in cross reactivities in terms of parallel dose response and dose inhibition to each other in hCG, alpha, and beta-subunits radioimmunoassays. The sialic acid content of hCG from the choriocarcinoma patient was undetectable, whereas the other two hCGs had about 8.5% sialic acid. Ovarian uptake of 125-hCG from the choriocarcinoma patient was approx 10% of the uptakes of the other two 125-hCG types, and agrees with low biological activity determined by the rat ovarian wt assay. Neoplastic or malignant transformation of trophoblasts may alter glycosylation, especially sialylation. (46 Refs)

13. ALTERATIONS IN THYROID HORMONE METABOLISM DURING CHEMOTHERAPY IN PATIENTS WITH TESTICULAR CARCINOMA.

Willemse PH, Sleijfer DT, Sluiter WJ, Schraffordt Koops H, Doorenbos H
Dept. Endocrinology, Internal Medicine, Univ. Hosp., Oostersingel 59, 9713 EZ Groningen, The Netherlands
Clin Endocrinol (Oxf); 16(3):303-313 1982

In a prospective study, the effects of chemotherapy on thyroid function in patients with non-seminoma testicular carcinoma were evaluated. Thirty-one patients were studied; in 16 immunoassayable HCG was present, but altered thyroid function could not be established. In 15 patients an exagger ated TSH response to TRH was observed. In these patients, although T3 and T4N values were normal, basal TSH levels were higher compared to patients with a normal TSH response, probably due to preceding lymphangiography. During chemotherapy, T4N, T3 and rT3 levels rose significantly, but basal TSH levels and the TSH response to TRH decreased. In contrast, the prolactin responses to TRH increased. The observed changes in thyroid function during chemotherapy appear to result from delayed thyroid hormone clearance, probably caused by an effect of chemotherapy on deiodinating enzyme activity. This would result, in an increase in T4N and rT3 levels and a fall in TSH levels and in the TSH response to TRH. Furthermore, after therapy the raised T4N and lowered TSH levels remained, whilst the FT3 level did not change either during or after therapy, suggesting an unaltered hypothalamic/pituitary axis. (Author abstract) (43 Refs)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

14. MONOCLONAL ANTIBODY AGAINST A MEMBRANE ANTIGEN CHARACTERIZING LEUKEMIC HUMAN B-LYMPHOCYTES.

Forster HK, Gudat FG, Girard MF, Albrecht R, Schmidt J, Ludwig C, Obrecht JP
Pharma Res. Div., F. Hoffmann-La Roche and Co., Ltd., Basel, Switzerland
Cancer Res; 42(5):1927-1934 1982

In the diagnosis of non-Hodgkin's lymphomas, the ready characterization of the neoplastic cell lineage by analysis of cell surface markers is of great importance. We present evidence for the existence of a human B-leukemia-associated antigen recognized by a complement-fixing monoclonal antibody (anti-Y 29/55). A hybridoma was produced by fusing mouse myeloma cells and splenocytes of a mouse immunized against lymphoid cells of a patient with B-cell chronic lymphocytic leukemia. Characterization of anti-Y 29/55-reactive normal and malignant leukocytes was demonstrated by cytolysis and indirect immunofluorescence. This revealed reactivity with an antigen on B-lymphoma cells (11 patients), on leukemic lymphocytes in B-cell chronic lymphocytic leukemia (13 patients), and on malignant cells in hairy-cell leukemia (2 patients) but not on leukemic cells of T-cell acute lymphoblastic leukemia (1 patient), on T-lymphoma cells (1 patient), on cells of acute myeloblastic leukemia (4 patients), or of chronic myeloid leukemia (4 patients). No specific cytolysis occurred with B- and T-peripheral blood lymphocytes from (a) healthy donors (16 individuals), (b) patient with reactive lymphocytosis (1 patient), (c) nonleukemic multiple myeloma (6 patients), or (d) Hodgkin's disease (3 patients). Surface immunoglobulin-positive, sheep RBC-negative lymphocytes isolated from human spleen (3 individuals), tonsils (7 individuals), and lymph nodes (1 individual), however, we recognized. It is concluded that leukemic B-cells carry a marker characteristic of nonrecirculating sessile B-lymphocytes. (Author abstract) (54 Refs)

15. THE PHENOTYPE OF THE NEOPLASTIC CELLS OF HAIRY CELL LEUKEMIA STUDIED WITH MONOCLONAL ANTIBODIES.

Jansen J, LeBien TW, Kersey JH
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Box 609 Mayo, 420 Delaware St. S. E., Minneapolis, MN, 55455
Blood; 59(3):609-614 1982

Eighteen cases of hairy cell leukemia were studied with a battery of polyclonal anti-Ig and nine monoclonal antibodies to determine the lineage of the hairy cells (HC) and the stage of their maturation arrest. Hairy cells tend to nonspecifically bind many antisera and precautions had to be taken to avoid nonspecific fluorescence of the cells. All but one case was reactive with one light chain type and one or more heavy chain isotype antisera as reported before. All cases studied were positive for monomorphic HLA-DR determinants, using monoclonal antibody 7.2. Most cases tested (6/7) were positive with the B-lineage related antibody PI 153/3. While most cases (15/18) were nonreactive with the B-lineage related antibody BA-1, they became positive (5/5) following in vitro culture. Seven out of nine cases were reactive with OKM1. Common acute lymphoblastic leukemia antigen (CALLA) was absent in all (15) cases tested and th ALL associated structure p24/BA-2 was absent from 16 of 18 cases. HC from none of the cases were clearly positive with the T-cell antibodies 9.6, or TA-1, whereas in only 1/18 the cells reacted with T101. The results of this study support the B cell lineage of most HC, and show the presence of multiple phenotypes. In combination with the surface Ig present on the cells, a hierarchy of phenotypes is postulated, with SIgormudelta, BA-1+, PI 153/3+, HLA-DR+ being the most immature, and SIg(alpha)gamma, BA-1-, PI 153/3-, HLA-DR+ the most mature. (Author abstract) (35 Refs)

16. LYMPH NODE T CELLS IN HODGKIN'S DISEASE: ANALYSIS OF SUSPENSIONS WITH MONOCLONAL ANTIBODY AND ROSETTING TECHNIQUES.

Aisenberg AC, Wilkes BM
Huntington Lab., Massachusetts General Hosp., Boston, MA, 02114
Blood; 59(3):522-527 1982

Suspensions prepared from lymph nodes involved by Hodgkin's disease and from a diverse group of lymph node hyperplasias were investigated with a panel of 10 monoclonal antibodies and a variety of conventional surface marker techniques. In both Hodgkin's disease and hyperplasia, 60%-70% of the cells were T lymphocytes, approximately 80% of the inducer/helper subset and 20% of the cytotoxic/suppressor subset. The most prominent differences observed between Hodgkin's disease and hyperplastic T cells are explained by greater affinity of the sheep cell receptor on the surface of the lymphoma T lymphocytes. This greater affinity was best demonstrated by the formation of rosettes with unsensitized or immunoglobulin-sensitized sheep erythrocytes after incubation at 37 C, an occurrence observed only with Hodgkin's disease cells. In addition, in hyperplasia, a variable proportion of lymphocytes reacting with the anti-T-cell monoclonal antiserum OKT3 failed to form unsensitized rosettes at 4 C (E rosettes), while in Hodgkin's disease there was near equivalence of T cells that reacted with the antiserum and formed E rosettes. In addition to the increased infinity for sheep erythrocytes, some Hodgkin's disease specimens displayed increased reactivity with the monoclonal antibody OKM1, which detects monocytes and granulocytes, and the monoclonal antibody OKT10, which reacts with early thymocytes. Finally, 14 of 20 lymphoma samples exhibited polar migration of the fluorescent material (capping) with one or more antisera (most frequently OKI1, the monoclonal antibody with specificity for the Ia-like antigen). These findings are useful in distinguishing Hodgkin's disease lymph nodes from hyperplasia by surface marker characteristics and may be relevant to older observations that Hodgkin's disease T cells aggregate about Reed-Sternberg cells. (Author abstract) (26 Refs)

17. NON-T, NON-B LYMPHOMAS ARE RARE IN CHILDHOOD AND ASSOCIATED WITH CUTANEOUS TUMOR.

Bernard A, Murphy SB, Melvin S, Bowman WP, Caillaud J, Lemerle J, Boumsell L
Laboratoire d'Immunologie des Tumeurs de l'Enfant, Institut Gustave-Roussy, 94800 Villejuif, France
Blood; 59(3):549-554 1982

Tumor cells from a total of 116 children with non-Hodgkin's lymphoma were studied for their pattern of reactivity with a battery of cell markers, including their capacity for spontaneous formation of sheep erythrocyte rosettes (E-rosettes), demonstration of surface immunoglobulins (SIg), and positivity with antisera against T-cell antigens, the common acute-lymphoblastic-leukemia-associated antigen (cALLa), and Ia-like antigens. Fifty-eight children (50%) had T-cell lymphomas, including all those with mediastinal tumors. Fifty children (43%)

had B-cell lymphomas, including 44 of the 45 with abdominal primaries. Eight children (7%) non-T, non-B tumors, four of whom presented at a young age with cutaneous lymphoblastic tumors. These results demonstrate that the great majority of children with NHL, not leukemic at diagnosis, have tumors clearly committed to either T- or B-cell differentiation pathways and only rarely exhibit the common ALL phenotype (cALLa+, Ia+, E-, T-, SIg-), contrasting with the distribution of childhood lymphoblastic leukemias. The unusual association of these non-T, non-B cases with skin involvement has not previously been reported, raising speculation regarding patterns of lymphocyte traffic and origins of childhood lymphomas and leukemias. (Author abstract) (32 Refs)

18. IMMUNOLOGICAL CHARACTERIZATION OF NON-HODGKIN'S LYMPHOMA: ENRICHMENT OF NEOPLASTIC CELLS FROM LYMPHOID TISSUES AND BLOOD.

Bom-Van Noorloos AA, Van Beek AA, Ubels-Postma J, Zeijlemaker WP, Van Heerde P, Von Dem Borne AE, Cleton FJ, Mellef CJ (c/o Mellef), Central Lab. Netherlands Red Cross Blood Transfusion Service, P. O. Box 9190, 1006 AD Amsterdam, The Netherlands
Cancer; 49(8):1605-1612 1982

Cell suspensions prepared from lymph nodes, spleen or peripheral blood of patients with non-Hodgkin's lymphoma (NHL) often contain a high percentage of residual nonmalignant cellular elements. By E-rosette sedimentation, it was possible to enrich such suspensions from patients with various types of lymphoma for malignant cells. In patients with a B- or non-B/non-T-cell lymphoma, the neoplastic cells were found in the non-T fraction. The capacity to respond to stimulation by various stimuli was then confined to the T-cell fraction, which contained the residual normal T-cells. In patients with T-cell lymphomas, in which the malignant cells had retained the capacity to form E-rosettes, lymphoma cells were found in the T fraction. These cells usually did not respond to mitogenic stimuli. Using this separation method, small proportions of neoplastic cells could be identified in mixed cell populations. Thus, in the blood from 9 out of 23 lymphoma patients without abnormalities in routine blood tests, a population of abnormal cells was detected after cell separation. This included a monoclonal B-cell population in the blood of four patients, a questionably monoclonal B-cell population in the blood of two patients and an increased non-B/non-T cell population in the blood of three patients. (Author abstract) (35 Refs)

19. IMMUNOPATHOLOGY OF CANCER OF THE LEFT COLON AND RECTUM. EVALUATION OF SOME PARAMETERS RELATED TO IMMUNOLOGIC RESPONSE OF THE HOST.

Naves A, Pollastri E, Dip O, Mancuso O, Puig N, Bravo Luna M, Amerio N, Morini JC
Centro de Onsologia, Hospital N del Centenerio, Rosario, Argentina
Rev Fac Cienc Med Univ Nac Rosario; 14(2):19-22 1981

Thirty patients (both sexes, 36-76 yr old) with cancer of left colon and rectum were treated by colectomy or coloproctectomy. Sections of original tumors, sections of tumors proximal and distal, and regional lymphatic ganglions (RLG) were examined. Staging according to TNM (tumor, lymph node, metastasis) indicated that 24 of the patients had neoplastic invasion reaching adipose tissue beyond muscle tissue and that 12 of the 24 had metastases in the RLG. Indexes of malignity of the tumors (IMT) were calculated, based on tumoral invasion, cortical and paracortical hyperplasia, local immune response (mononuclear cells in the border of the tumoral invasion), and perivascular lymphocytosis. Also at the time of diagnosis, peripheral blood was removed and concentrations of E rosettes were determined. The IMT was lower in patients who had curative surgery and was negatively correlated with age and with the concentration of E rosettes. It was concluded that local and general immunity of the host should be evaluated for better understanding of the physiopathology and evolution of the neoplastic process. (5 Refs) (In SPA)

20. SURFACE MARKERS ON LEUKEMIC BLASTS AND THEIR PROGNOSTIC SIGNIFICANCE.

Sen L, Estevez ME, Finiasz MR, Giuntoli J, Pavlovsky S, Sackmann-Muriel F, Divito J, Dibar E
Departamento de Microbiologia, Instituto de Investigaciones, Hematologicas, Buenos Aires, Academia Nacional de Medicina, Argentina
Medicina (B Aires); 41(Suppl):109-117 1981

A retrospective analysis of surface markers (SM) on bone marrow lymphoblasis from 148 patients (1 mo to 39 yr old) with untreated acute lymphoblastic leukemia (ALL) is reported; tests were on cells obtained by bone marrow aspiration at the time of initial diagnosis. Determination of SM included testing for receptors for sheep erythrocytes at 4 C (E4) and 37 C (E37), complement (C3), mouse erythrocytes (ME), and surface immunoglobulins (sIg). Seventy-one percent of the patients had no SM studied. Of the remaining 43 patients, 24 showed only one SM and 19 had two or more: the patients were subdivided into four different groups. T-ALL included E4 or E37 and/or C3, B-ALL included C3 and sIg, C3-All had only C3, and ME-ALL had only ME. T-ALL was predominant in boys greater than 5 yr old with high WBC, while C3-ALL prevailed in girls with WBC less than 50,000/cubic mm. Patients without markers were evenly divided between the sexes; 56% were 5 yr old or less, and WBC was 50,000/cubic mm or less. The relationship between SM and response to treatment, aggressivity, duration of remission, clinical features, and prognosis are analyzed. (45 Refs)

21. AMYL NITRITE MAY ALTER T LYMPHOCYTES IN HOMOSEXUAL MEN.

Goedert JJ, Wallen WC, Mann DL, Strong DM, Neuland CY, Greene MH, Murray C, Fraumeni JF, Blattner WA
Environmental Epidemiology Branch, NCI, Landow Building - Room 4C18, Bethesda, MD, 20205
Lancet; 1(8269):412-416 1982

To evaluate the recent outbreak of Kaposi's sarcoma (KS) and opportunistic infections in homosexual men, clinical, virological, and immunological data on 2 homosexual men with KS and on 15 healthy homosexual volunteers were collected. Both KS patients had regularly used amyl nitrite or butyl nitrite (AN); they had low helper/suppressor (H/S) T lymphocyte ratios before chemotherapy and high titers of antibody against cytomegalovirus (CMV). Eight of the 15 volunteers were regular AN users; 7 of the 8 had low H/S ratios due to larger than normal numbers of OKT8-positive suppressor cells and smaller numbers of OKT4-positive helper cells. In all eight AN users the fluorescence profile obtained with monoclonal antibody 9.6 (which detects the sheep E-rosette receptor) was bimodal, indicating a subpopulation of T cells with increased receptor density. A similar pattern was observed when OKT8, the antibody which detects cytotoxic suppressor cells, was used. Two of the seven men who did not use AN had abnormal fluorescence with reagent 9.6, and one of these also had a low H/S ratio. CMV-antibody titers were persistently high in 14 of the 15 healthy men, but the titers were not related to An use or T-cell abnormalities. The data suggest that nitrites may

be immunosuppressive in the setting of repeated viral antigenic stimulation and may contribute to the high frequency of KS and opportunistic infections in homosexual men. (Author abstract) (35 Refs)

22. T-CHRONIC LYMPHOCYTIC LEUKAEMIA PRESENTING AS PRIMARY HYPOGAMMAGLOBULINAEMIA - EVIDENCE OF A PROLIFERATION OF T-SUPPRESSOR CELLS.

Thien SL, Catovsky D, Oscier D, Goldman JM, Van Der Reijden HJ, Melief CJ, Rumke HC, Ten Berge RJ, Von Dem Borne AE
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Clin Exp Immunol; 47(3):670-676 1982

A 63-yr-old man with late onset hypogammaglobulinemia is described. Splenectomy, carried out because of marked splenomegaly and pancytopenia, demonstrated marked T lymphocytic infiltration in the splenic red pulp with prominent germinal centers. A persistent peripheral blood and bone marrow lymphocytosis ensued (10 x 10(9)/l and 40% respectively) and this was consistent with T-chronic lymphocytic leukemia (T-CLL). Over 88% of his blood lymphocytes were E+, OKT3+, OKT8+ and OKT11+; 54% of the T lymphocytes had receptors for IgG (Tgamma cells). Functional studies showed that the T lymphocytes of this parent lacked killer and natural killer cell function but they effectively suppressed the differentiation of normal B cells in a PWM stimulated system. It is suggested that the T-CLL in this patient resulted from the proliferation of the T suppressor subset which was responsible for his hypogammaglobulinemia. (Author abstract) (21 Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

23. THE SIGNIFICANCE OF THE TUMOR MARKERS ALPHA-FETOPROTEIN AND BETA-HCG IN STAGING AND MONITORING OF THE COURSE OF NON-SEMINOMATOUS TESTICULAR TUMORS.

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Therapiewoche; 32(5):525-531 1982

The presence of the tumor markers alpha1-fetoprotein (AFP) and beta-human chorionic gonadotropin (b-HCG) was measured regularly in serum of 277 patients with non-seminomatous tumors (NSTT) of the testicle at diagnosis and during the course of the disease. Among 230 evaluable patients at diagnosis AFP was detected in 58% and b-HCG in 53%. At least one of the markers was detected in 77% of the patients. S ignificant differences in serum levels of b-HCG and lactate dehydrogenase were found between patients in Stages I and IIA and those with more advanced disease. Comparison of serum marker levels before and after radical orchiectomy and retroperitoneal lymph node dissection required reclassification of 10/63 patients with Stage I or II tumors to higher stages. Marker levels in these patients remained elevated after surgery. Of 44 patients in complete remission, 20 showed a rise in marker levels an av 2.7 mo before clinical diagnosis of recurrence of NSTT. At 28 mo after treatment 84% of the 52 patients with Stage IIA disease were tumor-free. Of these patients 95% were with normalized marker levels, and 52% of the patients with abnormal marker levels were tumor free. Data indicate that measurement of AFP and b-HCG is a sensitive indicator for staging of NSTT, monitoring of the course of disease, and detection of recurrence. (10 Refs) (In GER)

24. PROGNOSTIC FACTORS IN CLINICAL STAGE I NON-SEMINOMATOUS GERM-CELL TUMOURS OF THE TESTIS.

Raghavan D, Peckham MJ, Heyderman E, Tobias JS, Austin DE
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Br J Cancer; 45(2):167-173 1982

Prognostic factors have been studied in 59 men with clinical Stage I non-seminomatous germ-cell tumors of the testis seen at the Royal Marsden Hospital between 1973 and 1978. Fourteen of the patients relapsed, and 45 have remained continuously disease-free. Two factors were identified which showed a significant correlation with relapse following radiotherapy: local extent of the primary tumor, and rate of decline of serum alpha-fetoprotein (AFP) and beta-human chorionic gonadotrophin (hCG) levels following orchidectomy. High serum marker levels at the time of referral after orchidectomy were not prognostically significant per se. The presence of tissue-associated hCG in the primary tumor was not prognostically significant. The results were compared with histology and pathological stage of the primary tumor in patients presenting with lung metastases but no clinical evidence of lymph-node disease. Embryonal carcinoma was more commonly associated with a locally invasive primary tumor and with extralymphatic spread than was teratocarcinoma. (Author abstract) (9 Refs)

25. SERUM-ALPHA1-FETOPROTEIN AND SERUM FERRITIN IN LIVER TUMORS.

Polterauer P, Linkesch W
II. Universitatsklinik fur Gastroenterologie und Hepatologie, Garnisongasse 13, A-1090 Wien, Austria
Wien Klin Wochenschr; 94(4):105-108 1982

Values of serum ferritin (SF) were evaluated in 22 patients (16 men, 6 women; 24-78 yr old) with histologically confirmed primary hepatic cancer (PHC); 11 patients had malignant hepatoma (MH) in liver without cirrhosis, 11 had MH associated with different hepatic pathologies; and in 25 patients (13 men, 12 women; 35-78 yr old) with histologically confirmed hepatic metastases (HM) from different primary cancers (12 large intestine, 5 pancreas, 3 stomach, and others). Radioimmunoassay was used for determination of alpha-1-fetoprotein (AFT) with normal values up to 9 nanog (ng)/ml. Heterologous antibody system was used for the determination of SF with the normal values 29-343 ng/ml (measured on 396 healthy controls). AFP values were elevated in 95.4% of PHC patients, but only 81.8% had values greater than 174 ng/ml, which were considered suspicious for PHC. SF values were elevated in 77.2% of PHC patients. Four of PHC patients had increased values of SF, although AFT values were low. SF values were elevated in 88% of HM patients, while AFT values were elevated only in 28%. Using both tests (SF and AFP) diagnosis of hepatic cancer would be increased. Elevated values for SF cannot differentiate between PHC and HM. (19 Refs) (In GER)

26. A SIMULTANEOUS STUDY OF FIVE MARKERS IN 80 CASES OF BREAST CANCER. CARCINO-EMBRYONIC ANTIGEN (CEA), FERRITIN BETA2, MICROGLOBULIN, (BETA M), SUB-UNIT BETA OF CHORIONIC GONADOTROPHIN HORMONE (BETA CGH) AND ALPHA FETOPROTEIN (AFP).

Fourrier E, Kadouche J, Mignot L, Reynier J, Gorins A, Rochet Y, Trevoux R, Gavel M

Centre des Maladies du Sein, Hopital Saint-Louis, 38, rue Bichat, F 75010 Paris, France

Gynecologie; 32(4/5):385-390 1981

Pathological levels of CEA, ferritin (FT), microglobulin (beta M), (CGH), and alpha fetoprotein (AFP) were compared in various stages of breast cancer (80 cases). When the pathologic level of CEA was set at 2.5 nanograms (nanog)/ml, there were positive results in 63% of the cases at diagnosis, 95% of the metastasized cancers, and 42% of the postoperative cases. When the pathologic level of CEA was set at 4 nanog/ml, the percentages of positive cases were 35%, 91%, and 35% respectively. In all cases, the highest positive values were obtained with CEA and FT. The value of beta M was more limited, and CGH and AFP provided very little information. In 18 metastasized cases which were treated with chemotherapy, CEA assays evolved along parallel lines with the clinical course of the disease in 16 cases and in 2 cases, levels of CEA increased while the disease seemed stable. FT evolved along clinical lines in 17 cases, but levels increased in 1 case which seemed to be in regression. The other assay results did not correlate in any significant way with clinical course of the disease. Based on the results of this study, it is recommended that CEA and FT be used to monitor the progress of patients who have been surgically treated for breast cancer and are undergoing adjvant therapy. (15 Refs) (In FRE)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

27. TOTAL AND LIPID-BOUND SIALIC ACID LEVELS IN SERA FROM PATIENTS WITH CANCER.

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Clin Chim Acta; 118(2/3):327-331 1982

Unhemolyzed serum samples from 45 healthy donors, 15 patients with diseases other than cancer, and 40 patients with malignant neoplasms of different histologic type, at different stages of disease, and from different organs, were examined for total sialic acid (TSA) and lipid-bound sialic acid (LBSA). LBSA determinations were made from unpartitioned lipid extracts. Average TSA values (millimole/liter serum) were: healthy donors were 1.94 +-0.2; patients with noncancer diseases 2.88 +-0.6; patients with malignant neoplasms 4.0 +-1.5. LBSA levels (micromole/liter serum) were, respectively: 28.6 +-5.9; 22.3 +-9.2; and 88.7 +-52.7. One-way analysis of variance established a significant difference between cancer and noncancer patients for both indicators. LBSA seems to be a better indicator, in the presence of malignancy, than TSA. (25 Refs)

28. SERUM COPPER LEVEL IN NON-HODGKIN'S LYMPHOMAS.

Salvagno L, Pappagallo GL, Sileni VC, Segati R, Cartei G, Endrizzi L, Paccagnella A, Ongaro G, Bonvicini P, Fiorentino MV

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Tumori; 68(1):57-62 1982

Serum copper level (SCL) was studied by the atomic absorption technique in 103 patients with non-Hodgkin's lymphoma. SCL was increased in 61% of patients at diagnosis or during active disease; values within normal range were found in 88% of patients in complete remission. The difference between means SCL during active disease and in remission was highly significant, independently of stage and histologic type, so that: (1) within the same clinical stage high SCL at diagnosis was associated with poorer response to therapy in Stage II and Stage III (respectively $p = 0.033$ and $p = 0.049$), but not in Stage IV, where the complete remissions were only 8 out of 42. A shorter 5-yr survival was also shown in Stages III and IV with high SCL at diagnosis (respectively p less than 0.025 and p less than 0.05), but not in Stage II where the deaths were only 3 out of 24. (b) within histologic types, SCL is a useful prognostic index of response to therapy and survival, although a statistically significant difference was only reached for poorly differentiated lymphocytic lymphoma. We conclude that SCL may be a good parameter of disease activity and a useful index of response to therapy and survival in non-Hodgkin's lymphoma. (Author abstract) (22 Refs)

29. DETECTION OF A SERUM DNA-BINDING PROTEIN ASSOCIATED WITH CANCER.

Galvan L, Evans JE, Comis RL, Gottlieb A, Gyorkey F, Lane M, Prestayko AW, Crooke ST

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Cancer Res; 42(4):1562-1566 1982

An accompanying report describes the purification and partial characterization o f a unique DNA-binding protein (Mr 64,000; pI 5.9) that is present in human sera. This report gives the results of assays of sera from patients from the bleomycin inhibitor protein (BIP) using the Pseudomonas bacteriophage covalently closed circular DNA fluorescence technique standardized for DNA breakage induced by bleomycin. The results of the BIP assays were expressed by values of specific activity of inhibition. One arbitrary unit of inhibitory activity was defined as equivalent to the amount of serum protein required to cause 50% inhibition of DNA degradation using standard conditions of the DNA breakage assay. The mean values of specific activity of inhibition (SAI) for groups of healthy individuals ($n = 26$), patients with nonmalignant diseases ($n = 33$), and patients with malignant diseases ($n = 88$) were 12.60 +-4.69 (SE), 12.53 + 3.17, and 2.40 +-0.84 units/mg, respectively. Mean SAI values for patients with cancers of various types were: solid tumors ($n = 46$), 2.44 +-0.86; leukemias ($n = 24$), 2.59 +-0.96; and lymphomas ($n = 18$), 2.07 +-0.64. The decrease in BIP activity was not correlated with sex, age, or prior chemotherapy. Mean SAI values of male ($n = 29$) and female ($n = 59$) patients with cancer were 2.61 +-0.87 and 2.30 +-0.83 units/mg, respectively. Mean SAI values for different age groups were: 0 to 40 yr ($n = 21$), 2.05 +-0.68 units/mg; 41 to 70 yr ($n = q6$), 2.59 +-0.68 units/mg; and greater than 70 yr ($n = 11$), 2.12 +-0.67 units/mg. Cancer patients with and without prior chemotherapy had mean SAI values of 2.97 +-0.85 ($n = 23$) and 2.20 +-0.86 units/mg ($n = 65$), respectively. Linear regression analysis comparing SAI values

and serum protein levels showed no correlation (r = 0.21). These results suggest that the decrease of the BIP is associated with malignant disease. Additional controlled studies are required before the significance of this association can be adequately assessed. (Author abstract) (21 Refs)

30. SERUM FERRITIN DURING THE COURSE OF CHRONIC MYELOID LEUKEMIA. INCREASE OF SERUM FERRITIN AS A MARKER OF DYSERYTHROPOIESIS.

Lang JM, Eber M, Methin G, Oberling F
Service des Maladies du Sang, Hopital de Hautepierre, 67098 Strasbourg Cedex, France
Acta Haematol (Basel); 67(3):145-149 1982

A solid-phase immunoradiometric assay for serum ferritin has been developed and applied to 30 patients with chronic myeloid leukemia (CML), including 13 patients with a typical chronic phase, 12 with bone marrow fibrosis without evidence of an acute phase and 5 with an acute phase. Patients were divided into three subgroups according to the erythrokinetic data as studied by the 59iron kinetic test. Serum ferritin was clearly correlated with the quality of erythropoiesis but not with blast cell mass nor white cell count. Given the prognostic value of dyserythropoiesis in the course of CML, serum ferr itin determination may be a helpful and simple parameter in the follow-up of CML patients. (Author abstract) (21 Refs)

31. PURINE AND PYRIMIDINE RIBONUCLEOSIDE MONOPHOSPHATE PATTERNS OF PERIPHERAL BLOOD AND BONE MARROW CELLS IN HUMAN ACUTE LEUKEMIAS.

Scavennec J, Maraninchi D, Gastaut JA, Carcassonne Y, Caillа HL
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Cancer Res; 42(4):1326-1330 1982

Purine and pyrimidine ribonucleoside monophosphate (NMP) levels were measured in blood and/or bone marrow cells of groups of patients with acute leukemia including acute lymphoblastic leukemia (ALL) and acute nonlymphoblastic leukemia (ANLL). Patients were either untreated or in remission. Three relapsed patients with ALL were also studied. Phytohemagglutinin-stimulated tonsil lymphocytes and bone marrow cells both from normal subjects were used as controls. Moreover, observations in acute leukemias were compared with those in chronic leukemias. The cytidine, adenosine, guanosine, and uridine 2'-, 3'-, and 5'-monophosphate contents were measured by high-performance liquid chromatography. 2'- and 3'-NMP concentrations were 2.5x higher in ALL and were 5.5x higher in ANLL leukemic cells than in chronic leukemic blood cells or control bone marrow cells. 2'-NMPs were found only in leukemic blast cells and accounted for about 30% of 2'- and 3'-NMP mixtures. Levels of 2'- and 3'-NMP were around two- and four-fold higher in bone marrow than in peripheral blood cells of patients. The high level of 2'- and 3'-NMP found in bone marrow and blood cells of untreated ALL patients decreased during remission without reverting to normal; however, in relapse, it was 5 to 10x higher than in the case of untreated patients. The 5'-NMP concentrations were always lower than those of 2'- and 3'-NMP and were the same in acute leukemias and controls. Furthermore, 5'-NMP levels remained constant during the course of the disease. 2'- and 3'-NMP levels appear therefore to be useful markers of leukemic blasts and may facilitate both the diagnosis of acute leukemia and the monitoring of chemotherapy. (24 Refs)

32. BLOOD LEVELS OF A PTERIDINE-BINDING ALPHA1-ACID GLYCOPROTEIN IN CANCER PATIENTS.

Fink M, Ziegler I, Maier K, Wilmanns W
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Cancer Res; 42(4):1574-1578 1982

A variant of alpha1-acid glycoprotein was found previously in blood of malignant cases. It had been characterized as a pteridine-binding alpha1-acid glycoprotein (P-AGPM). P-AGPM as well as the corresponding fraction of control origin were selectively enriched in the supernatant (Fraction b), obtained after digitonin extraction and subsequent alcohol and trichloacetic acid fractionation of whole blood. In Fraction b, alpha1-acid glycoprotein from control subjects + P-AGPM comprised 90 to 95% of total protein; it was quantitated by colorimetric determination of the protein-bound tyrosine and calibrated with the isolated compound. During a screening of malignant and nonmalignant cases, P-AGPM proved to be an acute-phase reactant to some extent. Marked increases during extended cancer and especially during leukemias corroborated the view that P-AGPM may be identical with abnormal orosomucoid. Longitudinal sections during leukemias suggested that the biopterin of leukemic cells may be metabolically related to the pteridine moiety of P-AGPM. Biopterin determinations by means of Crithidia assay in the blood of 136 cases of solid tumors showed that, due to its high rate of renal clearance, blood biopterin is not a reliable and persistent marker for proliferative activity, unless it is contained in the immature blood cells themselves, as is the case during leukemias. (Author abstract) (21 Refs)

33. A CANCER-ASSOCIATED MUCIN ALTERATION IN BENIGN COLONIC POLYPS.

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Gastroenterology; 82(4):664-672 1982

We have recently reported that the mucin in colon cancer is different from that in the normal colon, and this difference may be detected by selective lectin binding characteristics. The lectin Dolichos biflorus agglutinin (DBA) avidly binds to the mucin found in well-differentiated goblet cells in the normal colon, but does not bind to that in the majority of colonic cancers. Conversely, the lectin peanut agglutinin (PNA) does not bind to the mucin from the normal colon, but avidly binds to that in colon cancer. Therefore, these two lectins were used to determine if cancer-associated mucin were present in benign colonic polyps. Fluorescein isothiocyanate (FITC) conjugates of Dolichos biflorus agglutinin and peanut agglutinin were applied to fixed, unstained tissue sections of 56 colonic polyps and examined by fluorescent microscopy. Focal areas were found within the polyps in which FITC-DBA labeling was diminished (compared with the normal colon) and labeling with FITC-PNA appeared. The findings are expressed as the percentage of glands per polyp labeled by FITC-PNA. The median labeling in 31 benign tubular adenomas was 7% of the glands per polyp. In 16 benign tubular adenomas less than or equal to 7 mm in diameter, only 2% of the glands per polyp were labeled, while in 15 benign tubular adenomas greater than 7 mm in diameter, 24% of the glands per polyp were labeled. Carcinoma in situ or invasive carcinoma was found in nine adenomatous polyps, in which 41% of the adenomatous glands were labeled by FITC-PNA. Unexpectedly, in eight hyperplastic polyps, 89% of the glan ds were labeled by FITC-PNA.

These results indicate that among neoplastic colonic polyps, cancer-associated mucin changes are present and are more widespread in larger tubular adenomas, villoglandular adenomas, and adenomas containing cancer. The presence of mucin that is bound by FITC-PNA may be an indication of an increased risk of developing cancer within a colonic polyp. The finding of the cancer-associated mucin in hyperplastic polyps raises new questions about pathogenesis of these benign, apparently nonneoplastic lesions. (Author abstract) (27 Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

34. CATHEPSIN B ACTIVITY IN B16 MELANOMA CELLS: A POSSIBLE MARKER FOR METASTATIC POTENTIAL.

Sloane BF, Honn KV, Sadler JG, Turner WA, Kimpson JJ, Taylor JD
Dept. Pharmacology, Wayne State Univ., 540 E. Canfield, Detroit, MI, 48201
Cancr. Res; 42(3):980-986 1982

In solid sc tumors of a variant of the murine B16 melanoma with high metastatic potential (B16F10), there was a two- to seven-fold elevation of lysosomal cathepsin B activity when compared to the B16F1 variant with low metastatic potential. The highest activities (based on either protein or DNA) of cathepsin B were found in tumors of less than 1 g. When B16F1 and B16F10 melanoma variants were grown in tissue culture, the metastatic differential in cathepsin B activity was lost as the cells were subcultured. However, this differential in cathepsin B activity could be restored by reestablishing the cultured cells as sc tumors. The activities of four other lysosomal enzymes (cathepsin D, beta-N-acetylglucosaminidase, beta-glucuronidase, and acid phosphatase) showed little evidence of a positive correlation with the metastatic potential of the B16 melanoma variants Eighty to 90% of cathepsin B activity has been localized to a fraction containing viable tumor cells which was isolated by centrifugal elutriation. In contrast, only 50% of cathepsin D activity was in the viable tumor cell fraction, and from 30 to 70% of beta-N-acetylglucosaminidase, beta-glucuronidase, and acid phosphatase. Elevated levels of cathepsin B in the high metastatic B16F10 varient are consistent with the idea that cathepsin B may play a direct or a regulatory role in tumor metastasis. (Author abstract) (41 Refs)

35. IMMUNOCHEMICAL AND BIOLOGICAL CHARACTERIZATION OF CALCITONIN ORIGINATING FROM TRANSPLANTED MEDULLARY THYROID CARCINOMA IN RATS.

Myhre L, Ekeland A, Gautvik KM
Dept. Physiology and Biochemistry, Dental Faculty, Univ. Oslo, Oslo, Norway
Acta Endocrinol (Copenh); 99(3):397-403 1982

The immunoreactive and biological activities of calcitonin (CT) produced by transplanted rat medullary thyroid carcinomas (CT) produced by transplanted rat medullary thyroid carcinomas (MCT) have been studied. Immunoreactive CT (iCT) in serum and in MCT tissues of rats carrying tumors of g enerations 5-8 was characterized by gel filtration on Sephadex G-100 followed by radioimmunological measurements using region specific antiserum. The hypocalcemic effect of sera and tumor extracts was tested in a rat bioassay. Rats with transplanted MCT of the fifth and sixth generations had mainly (70-84%) circulating iCT species of molecular size comparable to intact hormone. However, in rats with tumors of the seventh and eighth generations corresponding circulating iCT forms comprised less than 52% of total immunoreactivity while 32-38% eluted earlier. In comparison, iCT corresponding to intact hormone represented 30-50% of total immunoreactivity in the tumor extracts and no differences were observed between the generations. Sc injections of sera from MCT rats and of tumor extracts reduced the serum levels of ionized calcium in test rats. The sera containing mainly intact iCT showed the strongest biological potency. We conclude that rat MCT transplanted under the kidney capsule is able to secrete biologicaly active CT. However, the heterogeneity of circulating iCT increases in rats with transplanted tumors of older generations, approaching the heterogeneity of stored hormone in the gland. (Author abstract) (35 Refs)

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Biological Markers

SERIES CT01 No. 82/09 SEPTEMBER, 1982

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. CARCINOEMBRYONIC ANTIGEN AS A MARKER IN PATIENTS WITH BREAST CANCER RECEIVING POSTSURGICAL ADJUVANT CHEMOTHERAPY.

Falkson HC, Falkson G, Portugal MA, Van Der Watt JJ, Schoeman HS
Dept. Cancer Chemotherapy, H. F. Verwoerd Hosp., Private Bag X169, Pretoria 0001, South Africa
Cancer; 49(9):1859-1865 1982

Serial plasma CEA levels were determined over a period of 1-3 yr in 114 patients receiving adjuvant chemotherapy for T1, 2 or 3a N+ MO breast cancer. CEA values were correlated with clinical status, scintiscans, and other biochemical parameters. CEA values greater than 2.5 ng/ml were considered abnormal. Forty-one patients had normal values throughout the adjuvant period. In 73 patients where abnormal values occurred, four different patterns were seen: (1) a statistically significant number (30/73) had initial elevations with a decreasing titer; (2) rising titer (10/73); (3) fluctuating titer of transient elevation (25/73); and (4) persistent elevation (8/73). Seventeen patients developed overt metastases, this was associated with a rising CEA in nine patients (p less than 0.002). CEA was more sensitive for predicting relapse than alkaline phosphatase of LDH. The correlation between CEA determination and the eventual development of metastatic disease is striking, and has implications for the design of future clinical trials. Results indicate that CEA could be used to identify high risk patients, to estimate efficacy of chemotherapeutic regime, and to determine optimal duration of therapy. (Author abstract) (9 Refs)

2. CEA POSITIVITY IN TISSUE AND SERA OF PATIENTS WITH BENIGN BREAST LESIONS.

Wittekind C, Von Kleist S, Sandritter W
Institut fur Immunobiologie, Stefan-Meierstrasse 8, D 7800 Freiburg, W. Germany
Oncodev Biol Med; 2(6):381-390 1981

The presence of CEA was studied in paraffin sections of 100 benign breast lesions using an immunoperoxidase technique. In fibroadenomas, CEA was found in 25% of cases as opposed to 64% with cystic disease with or without epitheliosis. Our results demonstrate a tendency for an increased frequency of CEA tissue positivity in association with a more prominent form of epithelial hyperplasia with cystic disease. The observed higher positivity of tissue CEA may reflect a higher 'cellular activity' in the latter lesions compared with fibroadenomas. (Author abstract) (25 Refs)

3. CARCINOEMBRYONIC ANTIGEN SERUM LEVELS IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX: CLINICAL SIGNIFICANCE.

te Velde ER, Persijn JP, Ballieux RE, Faber J
Dept. Gynecology, Univ. Hosp., Catharijnesingel 101, 3500 CG Utrecht, The Netherlands
Cancer; 49(9):1866-1873 1982

In 114 patients with invasive cervical cancer of the squamous cell type pretreatment CEA levels were determined. An individual upper limit of the normal range was derived taking into account the smoking habits and the age of each patient. Pretreatment CEA levels exceeding the upper limit of normal concurred with a very poor prognosis, regardless of the stage of the tumor. Moreover, in 92 patients longitudinal CEA patterns were established. The median follow-up time of the nonrecurrence patients was 4 yr. Three patterns appeared to be exclusively associated with the presence of recurrent cancer. The median lead-time obtained in patients demonstrating such patterns, was 13 wk. The clinical value and the possible therapeutic consequences of the findings presented are discussed in relation to the available knowledge of tumor growth in cervical cancer. (Author abstract) (39 Refs)

4. CEA SERUM VALUES CONTROVERSY.

Satler JJ, Herzog B
Medical Dept. Gastroenterology, Univ. Ljubljana, 2 Japljeva, 61000 Ljubljana, Yugoslavia
Am J Proctol Gastroenterol Colon Rectal Surg; 33(2):24,26,28 1982

Considering the hypothesis that the CEA concentrations in serum might be in proportion with CEA concentrations in malignant tissue of patients with proven colorectal carcinoma, thus explaining different normal as well as pathological values in sera, 23 radically operated patients were selected for the study. Both concentrations were estimated using radioimmunoassay of double antibodies and the values of every single patient compared. No correlation was established as in spite of high CEA productive tumors the levels of CEA concentrations in sera were found to be within normal as well as pathological range. Parallel to this study, CEA concentrations in sera and ascites of 37 patients were compared using the same method. While in malignant ascites the levels of CEA concentration were always high in the pathological range over 100 ng, the levels in sera were within normal limits in four out of seven patients. In ascites of 27 patients with liver cirrhosis CEA concentrations were always low to 30 ng/ml. It could be concluded that the reason for disproportion between carcinoembryonic antigen concentrations is highly productive malignant tissue and moderate, even normal values in sera still remains obscure and controversial. On the other hand it suggested that the estimation of CEA concentrations in ascitic fluid might be more useful for differentiating the malignant from nonmalignant ascites than CEA concentrations values in sera. (Author abstract) (7 Refs)

5. SERUM LEVELS OF CARCINOEMBRYONIC ANTIGEN AND A TUMOR-EXTRACTED CARCINOEMBRYONIC ANTIGEN-RELATED ANTIGEN IN CANCER PATIENTS.

Shively JE, Spayth V, Chang FF, Metter GE, Klein L, Presant CA, Todd CW
Div. Immunology, City of Hope Res. Inst., Duarte, CA, 91010
Cancer Res; 42(6):2506-2513 1982

Levels of carcinoembryonic antigen (CEA) and a tumor-extracted CEA-related antigen (TEX) were determined in sera from patients with carcinomas of the breast, colon, lung, head and neck, and a number of miscellaneous categories. The purpose of this study was to compare the levels of each antigen at various stages of malignant disease. Competitive radioimmunoassays developed in our laboratory were shown to be sufficiently specific to detect either of these two antigens independent of each other. The results indicate that: (a) with our specific assays, CEA was not significantly elevated in smoker controls, but TEX was elevated in 29% of smoker controls; (b) TEX was equivalent to CEA as a tumor marker for colonic cancer. TEX was better than CEA as a marker for lung cancer and, based on limited data, there is a possibility that TEX is a significantly better tumor marker than is CEA in early lung cancer; (c) TEX was superior to CEA as a tumor marker for

breast and head and neck cancers; (d) there is a strong indication that serial determinations of TEX can be used as effectively as CEA in the monitoring of disease progress. These preliminary results must be confirmed by increasing the number of cancer patients and including nonmalignant disease controls. (Author abstract) (18 Refs)

6. ENDODERMAL SINUS TUMOUR OF THE OVARY: THE PLACE OF ALPHAFETOPROTEIN DETECTION, SURGERY AND CHEMOTHERAPY.

Khoo SK, Buntine DW, Massay PF, Jones IS
Dept. Obstetrics and Gynaecology, Univ. Queensland, Brisbane, Australia
Aust NZ J Obstet Gynaecol; 21(4):217-225 1981

Two white females 36 (A) and 34 (B) yr old were treated by CHAMOA chemotherapy after an assay of a unilateral salpingo-oophorectomy revealing an endodermal sinus tumor. Progress was followed by weekly serum alphafetoprotein (AFP) assay. The chemotherapy consisted of four monthly 9-day courses of hydroxyurea, vincristine, methotrexate, citrovorum factor, cyclophosphamide, and adriamycin D. Case A has been in remission over 2 yr after a 2nd laparotomy and total hysterectomy 8 mo after presentation. Case B developed metastases to the peritoneum, omentum, and para-aortic nodes shortly after the last course. After total hysterectomy, chemotherapy consisted of four monthly 15-day courses of vinblastine, bleomycin, and cis-diaminedichloroplatinum. This subject has also been in remission for 2 yr. In both cases the AFP became undetectable during the 1st or 2nd CHAMOA course. In case B AFP rose rapidly after the 4th course and was the occasion for the discovery of the metastases on laparotomy. Reports of diagnosis, chemical and surgical treatment, and prognosis for this tumor are reviewed. Diagnosis should be restricted to immunohistochemical staining strongly positive only for AFP, and not for carcinoembryonic antigen or human chorionic gonadotrophin. (35 Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

7. PLACENTA-LIKE ISOENZYME OF ALKALINE PHOSPHATASE IN PROSTATIC CANCER.

Schmidt JD, Slack NH, Chu TM, Murphy GP
Div. Urology H-897, Univ. California Medical Center, 225 Dickinson St., San Diego, CA, 92103
J Urol; 127(3):457-459 1982

Assays for serum placenta-like (Regan) isoenzyme of alkaline phosphatase were done on 157 samples from 96 patients with prostatic cancer entered into various National Prostatic Cancer Project protocols. Elevated placenta-like isoenzyme levels were found in 19 patients (20%). Increased isoenzyme activity was seen in some patients with early clinical stages of the disease (B1 and B2), as well as in those with advanced disease. As in other reports results were not consistent in any individual patient. No correlations could be made between elevated isoenzyme activity and either stage of the disease or response to therapy. The placenta-like isoenzyme of alkaline phosphatase appears to be a nonspecific oncodevelopmental marker that is not helpful alone as a diagnostic indicator but that may be promising as part of a profile of markers for a patient with prostatic cancer. (Author abstract) (10 Refs)

8. DEVELOPMENT AND EVALUATION OF A NEW SOLID-PHASE DIRECT IMMUNOENZYME ASSAY FOR PROSTATIC ACID PHOSPHATASE.

Gericke K, Kohse KP, Pfleiderer G, Fluchter SH, Bichler KH (c/o Pfleiderer) Inst. Organic Chemistry, Biochemistry and Isotope Res., Univ. Stuttgart, Pfaffenwaldring 55, D-7000 Stuttgart 80, W. Germany
Clin Chem; 28(4):596-602 1982

In this assay we used polystyrene-tube-attached rabbit antibodies against prostatic acid phosphatase (PAP) that had been purified to homogeneity from human prostate. The amount of immunoreactive acid phosphatase was determined directly by its enzymic activity in the solid-phase-bound immune complex. The detection limit was 0.05 U/L (0.13 ug/L), the CVs between 4.3 and 10.8%. Investigating the organ specificity of PAP, we found that some cross-reacting acid phosphatase activity could be so measured in human kidney, leukocytes, and platelets, all of which probably contribute to the circulating 'prostatic' acid phosphatase that normally is present in serum. Diurnal and day-to-day variations in serum PAP activity were as much as 100% in healthy subjects. Individuals without prostatic diseases (n = 92) had values from serum PAP activity up to 0.36 U/L (0.94 ug/L), in an age-independent distribution; patients with benign prostatic hyperplasia (n = 62) showed values up to 0.48 U/L (1.25 ug/l). With PAP activity of 0.38 U/L or 1.0 ug/L (90th percentile of the prostatic group) as the upper limit of 'normality,' overall sensitivity (stages A-D) for detection of prostatic cancer in 33 essentially untreated patients was 65%. Examples for the followup of therapy of prostatic cancer by measurement of serum PAP with this assay are described. (Author abstract) (34 Refs)

9. SERUM ALKALINE DEOXYRIBONUCLEASE IN ORAL CANCER AND PREMALIGNANT LESIONS.

Scully C, Spandidos DA, Ward-Booth P, McGregor IA, Boyle P
Univ. Dept. Oral Medicine and Pathology, Glasgow Dental Hosp. and Sch., 378, Sauchiehall St., Glasgow, Scotland
Biomedicine [Express]; 35(6):179-180 1981

Serum activities of alkaline deoxyribonuclease were assayed in 61 patients with oral squamous cell carcinoma, 23 with oral keratosis (a possible premalignant lesion), and 48 matched controls. The activity of alkaline deoxyribonuclease was significantly greater in patients with oral cancer than in either those with oral keratosis, or controls. The activities of deoxyribonucleases in keratosis were greater than in controls but not at a significant difference. (Author abstract) (16 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

10. LACK OF CORRELATION OF A HISTOCHEMICAL METHOD FOR ESTROGEN RECEPTOR ANALYSIS WITH THE BIOCHEMICAL ASSAY RESULTS.

Panko WB, Mattioli CA, Wheeler TM
Dept. Pathology, Baylor Coll. Medicine, Houston, TX, 77030
Cancer; 49(10):2148-2152 1982

Forty-nine specimens of carcinoma of the breast were analyzed for estrogen receptor content using the sucrose gradient method and a histochemical method using a conjugate of estradiol (6-BSA-Fluor-CMO-17beta-estradiol). The specimens analyzed by the histochemical method were graded for fluorescent

intensity, percentage of cells fluorescing, and cellularity. Only 53.1% (26/49) of the specimens were classified into the same three categories (positive, negative and ambiguous) as classified by the biochemical assay. If the negative and ambiguous categories were combined, the degree of correspondence rose to only 63.3% (31/49). Because the classification scheme was arbitrary and because the results of the biochemical assay might be correlated with one or more factors, univariate and multivariate analyses were used to examine the data for any underlying relationships. Only the age of the patient was significantly correlated with the results of the biochemical assay. Importantly, neither the percentage of cells fluorescing nor the fluorescent intensity was correlated with the results of the biochemical assay. Terms to account for various interactions of parameters did not enhance the association with the biochemical results. While this histochemical assay may eventually prove to be effective in selecting patients for endocrine therapy, it does not seem to be a substitute for the standard biochemical assay for estrogen receptors presently used. (Author abstract) (11 Refs)

11. ASSAY OF ESTRADIOL RECEPTORS IN HUMAN BREAST CARCINOMAS USING THE GAMMA EMITTING LIGAND 16ALPHA[125I]IODOESTRADIOL.

Duffy MJ
Dept. Nuclear Medicine, St. Vincent's Hosp., Dublin 4, Ireland
J Steroid Biochem; 16(2):343-344 1982

The use of 16alpha[125I]iodoestradiol to assay estrogen receptor (ER) in human breast carcinoma was investigated. A constant amount of cytosol was incubated at five different concentrations of radiolabeled estradiol overnight at 4 C, and nonspecific binding was measured with parallel incubations in the presence of 100-fold excess unlabeled diethylstilbestrol (DES). Excess unlabeled estradiol and DES were the most potent inhibitors of binding, estrone and estriol were less potent, and testosterone, progesterone, and cortisol were ineffective. The affinity of iodoestradiol for breast tumor ER was similar to that of tritiated estradiol in 19 carcinoma cytosols. Good agreement was found between results using tritiated and iodoestradiol as ligands (correlation coefficient = 0.97). Twelve tumors contained less than 50 femtomoles ER by both ligands. Good agreement was observed between the use of a single saturating concentration of 5 nanoM iodoestradiol and the Scatchard plot analysis using the same ligand (correlation coefficient = 0.97). Advantages of using a gamma-emitting ligand for the assay of ER in breast tumor tissue are listed. (4 Refs)

12. MICROASSAY OF HORMONAL RECEPTORS BY NEEDLE BIOPSY IN HUMAN BREAST LESIONS AND TUMORS. DETERMINATION OF ESTROGEN RECEPTORS.

Delarue JC, Mouriesse H, Contesso G, May-Levin F, Sancho-Garnier H
Institut Gustave-Roussy, Rue Camille-Desmoulin, 94800 Villejuif, France
Biomedicine; 34(3):153-160 1981

Estrogen receptors measurement was assayed in human mammary tumors as well as corresponding fine needle aspiration biopsies (95 cases). Correlations between these two determinations were highly significant just as correlations between aspiration biopsies of the same tumor. Some factors may disturb the quality of aspiration biopsy results particularly: a low number of tumoral cells expressed by the cell density, ratio: sample weight-cytosol volume lower than 1/17 corresponding to a too great dilution, a sample weight lower than 20 mg. (Author abstract) (13 Refs) (In FRE)

13. DOES PROGESTERONE RECEPTOR IN HUMAN BREAST CANCER REFLECT THE MAST-CELL CONTENT OF THE TUMOUR TISSUE?

Thoresen S, Thorsen T, Hartveit F
Norwegian Cancer Society, Univ. Bergen, Bergen, Norway
Br J Cancer; 45(4):618-620 1982

Material from surgical specimens of patients (33-91 yr old) with infiltrating breast carcinomas treated by modified radical mastectomy was analyzed to determine whether progesterone receptor (RP) content reflects the mast-cell content. All PR negative (RP-) estrogen receptor negative (RE-) cases (17), RP-RE+ cases (18), and the first 29 RP+RE+ cases were examined. The mean values for the mast-cell count were related to the receptor profile of the tumors as judged from cytosol assay. The profile RP+RE- was not included since there were only three such cases. When the range and distribution of the mast-cell count was determined, great scatter was observed in all groups. A line dividing the material at 40 mast cells/20 high-power fields divided the RP-RE+ group almost in half, while only one value was over 40 in each of the other groups. In the 29 tumors with the common profile RP+RE-, the mean mast-cell count in 20 high-power fields was 13 +-14; that in the RP-RE+ group of 17 tumors was similar: 8 +-16. The mean mast-cell count was significantly higher in the 18 tumors with the profile RP-RE+. No relationship was found between the exact RP values and the mast-cell counts. Tumor mast cell content should be considered before a negative RP report is accepted. (15 Refs)

14. CORRELATION OF PROSTATIC NUCLEAR ANDROGEN RECEPTOR CONTENT WITH DURATION OF RESPONSE AND SURVIVAL FOLLOWING HORMONAL THERAPY IN ADVANCED PROSTATIC CANCER.

Trachtenberg J, Walsh PC
Dept. Urology, Royal Victoria Hosp., 687 Pine Ave. West, Montreal, Quebec, H3A 1A1, Canada
J Urol; 127(3):466-471 1982

To assess whether pretreatment prostatic androgen receptor measurements would be of value in predicting the response to hormonal therapy in patients with prostatic cancer 23 men with metastatic carcinoma of the prostate underwent prostatic biopsy before treatment. Cytosolic and nuclear prostatic androgen receptor contents were measured by a single saturating dose, dextran-charcoal assay. All patients had measurable levels of androgen receptor in prostatic tissue and all demonstrated objective evidence of improvement following hormonal therapy. Thus, if androgen receptor measurements are to be useful in predicting prognosis correlations between quantitative levels of receptor and quantitative aspects of response must be established. In our study response was quantitated by measuring the duration of response and survival following hormonal treatment. The strong correlation between duration of response and survival (p less than 0.01) demonstrated herein suggests that survival in these patients is related directly to the duration of time patients respond to hormonal therapy. Neither total cellular nor cytosolic androgen receptor content correlated with response. However, nuclear androgen receptor content correlated with the duration of response and survival following hormonal treatment (p less than 0.05). Furthermore, in patients with nuclear receptor levels less than 110 fmol per mg deoxyribonucleic acid the duration of response (7.1 plus or minus 3.8 mo) and survival (14.4 plus or minus 5.9 mo) was significantly shorter than in patients with higher levels of nuclear receptor

(17.3 plus or minus 10.4 and 24.7 plus or minus 8.8 mo, respectively (p less than 0.05)). These findings, which are the first report of a correlation between nuclear androgen receptor content and hormonal responsiveness, suggest that measurements of nuclear receptor may aid in identifying those patients unlikely to obtain prolonged response from hormonal therapy. (Author abstract) (25 Refs)

15. RADIOIMMUNOASSAY FOR THE MIDDLE REGION OF HUMAN PARATHYROID HORMONE USING AN HOMOLOGOUS ANTISERUM WITH A CARBOXY-TERMINAL FRAGMENT OF BOVINE PARATHYROID HORMONE AS RADIOLIGAND.

Mallette LE, Tuma SN, Berger RE, Kirkland JL
c/o Dr. L. E. Mallette, Medical Service (111E), Veterans Admin. Medical Center, 2002 Holcombe Blvd., Houston, TX, 77211
J Clin Endocrinol Metab; 54(5):1017-1024 1982

A new type of RIA for human parathyroid hormone (hPTH) is described. The antiserum was generated in a goat against hPTH, and the radioligand is a carboxy-terminal fragment of bovine PTH (bPTH). Although the antiserum is bivalent, use of the fragment as tracer yields an assay monospecific for the midregion of the PTH molecule. The assay can detect 0.3 fmol/tube of intact hPTH-(1-84) or 0.1 fmol synthetic hPTH-(44-68), but does not detect hPTH-(1-34), hPTH-(53-84), or bPTH-(28-48). Immunoreactive PTH (iPTH) was detectable in 85 of 92 normal subjects, with a normal range of about 0.1-0.5 microU/ml hPTH Research Standard 75/549. iPTH was undetectable in 22 consecutive severely hypoparathyroid patients and was above normal in 147 of 158 patients with primary hyperparathyroidism. In 60 patients with nonparathyroid hypercalcemia, iPTH averaged 20% lower than in normal subjects, but was still detectable in 80%. Mean iPTH values in hypercalcemia due to malignancy or other nonparathyroid causes were indistinguishable. When renal insufficiency supervened in those with nonparathyroid hypercalcemia, iPTH tended to increase, and reached levels three- to four-fold above normal when serum creatinine was above 5 mg/dl. In chronic renal failure, iPTH levels were 5-to 36-fold above normal in patients just beginning hemodialysis and 60-to 600-fold evaluated in those with severe osteitis fibrosa. The distribution of iPTH values in hypercalcemic chronic hemodialysis patients was bimodal; values were about 600-fold elevated in patients whose hypercalcemia responded to parathyroidectomy (tertiary hyperparathyroidism), but only 2-to 20-fold increased in those with nonparathyroid hypercalcemias. The assay was sensitive enough to detect changes that occurred spontaneously in normal subjects or were induced by EDTA infusion. The assay was also useful in detecting venous of PTH. This new assay, with its excellent sensitivity, provides a useful diagnostic and research tool for studies of human parathyroid function. (Author abstract) (33 Refs)

16. THE ROLE OF HUMAN CHORIONIC GONADOTROPIN IN SEMINOMATOUS TESTICULAR TUMOR.

Masuda M
Dept. Urology, Sch. Medicine, Kobe Univ., Japan
Hinyokika Kiyo; 28(1):1-12 1982

In order to investigate the significance of human chorionic gonadotropin (hCG) in seminoma of the testis, serum hCG levels in peripheral and testicular venous bloods before orchiectomy and hCG levels in tumor tissues were measured in 25 cases. Additionally, tissue specimens of seminomas were immunohistochemically studied for the cellular location of hCG by peroxidase antiperoxidase (PAP) method. The results were as follows: The rates of elevation of serum hCG levels were 47.8% in peripheral venous blood, and 88.8% in testicular venous blood. HCG levels in tumor tissues were detected in all cases, and their average level was 437.6 ng/g tissue. In case hCG levels in tumor tissues were less than 150 ng/g tissue, serum hCG were negative both in testicular and peripheral venous bloods. However, in case showing the level more than 150 ng/g tissue, serum hCG in testicular venous blood were positive, and if more than 200 ng/g tissue, serum hCG in peripheral venous blood were positive in all cases. By PAP method, hCG was demonstrated within syncytiotrophoblastic giant cell (STGC) in 10 of 22 cases, and in 2 cases of 10, cellular localizations of hCG were found not only in STGC but also in tumor cells of seminoma. In the positive group by PAP method, both serum hCG levels and rates of elevation of serum hCG levels in peripheral and testicular venous bloods were higher than the negative group. And the same result was obtained in hCG levels in tumor tissues. It was concluded that the measurement of serum hCG levels in peripheral venous blood before orchiectomy is useful as a serum marker for seminoma. STGC were mostly seen by PAP method in the cases which showed high hCG levels before orchiectomy among the cases diagnosed as pure seminoma histopathologically by hematoxylin-eosin stained specimens. Those should be regarded as non-seminomatous germ cell tumors. (Author abstract) (40 Refs) (In JPN)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

17. CELL-SURFACE A, B, OR H-BLOOD-GROUP ANTIGENS IN UROTHELIAL CANCER.

Newman AJ, Graham MA, Carlton CE
Roy and Lillie Cullen Dept. Urologic Res., Baylor Coll. Medicine, Houston, TX
Cancer Bull; 34(1):7-9 1982

In order to evaluate the prognostic significance of the presence or absence of surface A, B, or H antigens in superficial bladder tumors, a retrospective longitudinal analysis of A, B, or H blood group antigens was performed on 516 bladder tumor specimens collected during the period 1955 to 1972 from patients with Stage A disease. The specific red cell adherence (SRCA) technique was used. A strong correlation was apparent between the presence or absence of A, B, and H group antigens and the propensity for recurrence with invasion in patients with superficial bladder tumors. Only 4% of the patients with lesions initially positive for SRCA subsequently developed invasive lesions, whereas 71% of the patients with initially negative SRCA tests ultimately had invasive cell carcinoma. Of the Grade I and II lesions that were negative for SRCA, 71% became invasive, compared to 75% of the Grade III lesions with initially negative SRCA results Regardless of the source of tissue containing carcinoma in situ (CIS) or dysplasia (cystectomy specimen for invasive disease or biopsy near a superficial tumor), the vast majority of these areas showed deletion of A, B, or H antigens, indicating that the SRCA reaction has no value in predicting the subsequent clinical course of CIS or dysplasia. Prospective studies of the SRCA test and increased sensitivity for patients with blood type O must be accomplished before established therapies are altered. (13 Refs)

18. MONOCLONAL ANTIBODY AGAINST EBV-ASSOCIATED TRANSFORMATION ANTIGEN DETECTED IN VITRO AND IN VIVO.

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Protides Biol Fluid Proc Colloq; 29:739-742 1982

Transformation antigens on the surface of in vitro Epstein-Barr virus (EBV)-transformed B lymphocytes were defined by producing specific monoclonal antibodies. A hybridoma (17D6) was cloned and analyzed for its binding properties to a variety of EBV-positive and -negative B cell lines. The antibody reacted strongly with all of the EBV-positive lines and weakly with the EBV-negative lines. Similarly, a panel of EBV-negative cell lines from a variety of sources reacted only weakly with the 17D6 antibody. When a whole panel of EBV-infected cells from sources other than in vitro infection were tested, all the cell lines containing EBV were as positive as in vitro infected cells, including one cell line derived by spontaneous outgrowth from an EBV-positive individual and one from co-cultivation of normal lymphocytes from a seronegative individual with a nasopharyngeal carcinoma. Burkitt's lymphoma tumor cells reacted only weakly with the 17D6 antibody due to their relatively low levels of the antigen. 17D6-positive cells also were detected in the peripheral blood of infectious mononucleosis (IM) patients. 17D6-positive cells could be detected in the peripheral blood of a patient with chronic EBV infection at higher levels than in patients with acute IM. After recovery, no 17D6-positive cells could be detected. Radioimmunoprecipitation studies suggested that the 17D6 antibody recognizes a polypeptide of 40,000 mol wt. The results indicated that the 17D6 antibody recognizes an EBV-associated transformation antigen on the surface of in vitro and in vivo infected cells. (4 Refs)

19. A MONOCLONAL ANTIBODY DEFINING A BURKITT LYMPHOMA ASSOCIATED ANTIGEN.

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Protides Biol Fluid Proc Colloq; 29:899-902 1982

Reactivity of monoclonal antibody 38-13, obtained by using murine myeloma cells with Lewis rat splenocytes sensitized with Daudi cells (human Burkitt lymphoma), was investigated. Negative results were obtained in all patients with B chronic lymphoid leukemia, acute lymphoid leukemia (T and nonT-nonB), acute myeloid leukemia, acute monoblastic leukemia, Hodgkin's disease, T cell lymphosarcoma, and B cell lymphosarcoma (nodular and diffuse). Positive results were observed in 4/8 patients with B cell Burkitt lymphoma. When the specific reactivity of 38.13 ascites was tested with a panel of cell lines of various origins, both by complement dependent lymphocytotoxicity tests and indirect membrane immunofluorescence assays, all the positive target cells were of Burkitt's lymphoma origin. Negative results were obtained with 15 Epstein-Barr virus positive lymphoblastoid cell lines, 4 T cell lines, a chronic myelogenous leukemia cell line, 4 teratoma cell lines, and one each of melanoma and neuroblastoma. The 38.13 monoclonal antibody may be useful for diagnosis and specific immunotherapy of Burkitt lymphomas. (8 Refs)

20. MOLECULAR HETEROGENEITY OF A HIGH MOLECULAR WEIGHT HUMAN MELANOMA ASSOCIATED ANTIGEN DETECTED BY MONOCLONAL ANTIBODIES.

Imai K, Wilson BS, Ruberto G, Nakanishi T, Yachi A, Ferrone S

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Protides Biol Fluid Proc Colloq; 29:893-897 1982

The spatial relationship among antigenic determinants recognized by four monoclonal antibodies (MoAbs) specific for a human high mol wt melanoma-associated antigen (MAA) was analyzed. The four MoAbs were compared in direct and indirect inhibition binding assays to determine whether they identified the same or different antigenic determinants. MoAbs 138.13S, 225.28S, and 653.40S recognized the same or closely associated antigenic determinants which were distinct from that recognized by MoAb 763.24T. Sequential immunodepletion studies demonstrated that the high mol wt MAA may be divided into three subpopulations: Group 1 carries the antigenic determinants recognized by the MoAb 138.13S (225.28S or 653.40S) and 763.24T; Group 2 carries only the determinants recognized by MoAb 138.13S (225.28S or 653.40S); and Group 3 carries only the determinants recognized by the MoAb 763.24T. The amount of high mol wt molecules in each subpopulation was in the order of Group 1 greater than Group 2 greater than Group 3. (7 Refs)

21. TISSUE DISTRIBUTION AND MOLECULAR PROFILE OF A DIFFERENTIATION ANTIGEN DETECTED BY A MONOCLONAL ANTIBODY (345.134S) PRODUCED AGAINST HUMAN MELANOMA CELLS.

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Cancer Immunol Immunother; 12(2):159-166 1982

The mouse IgG2a monoclonal antibody (MoAb) 345.134S secreted by a hybridoma derived from a mouse immunized with cultured human melanoma cells was examined in relation to the structure of the target antigen, the distribution of the antigen in normal and malignant tissues, and the expression of the antigen on cultured cells and its ability to function as a target of immune lysis. The structure detected by the MoAb 345.134S is composed of an 85 kilodalton (KD) glycopolypeptide linked by disulfide bridges with a 30 KD polypeptide carrying little or no carbohydrate. The 115 KD antigen appears to be peripheral rather than integral to the plasma membrane. Indirect immunofluorescence studies showed that the reactivity pattern of normal tissues with MoAb 345.134S does not correlate with their embryological origin. The majority of normal tissues gave only weak staining with MoAb 345.134S. All the types of tumors tested, except liver adenocarcinomas, reacted strongly with MoAb 345.134S, although there were some cases within each tumor group that were negative. MoAb 345.134S reacted in a radioimmunometric assay with a variety of cell lines, including melanoma, carcinoma, and lymphoid types. There was no relationship between the level of expression of the antigenic determinant recognized by MoAb 345.134S and other surface markers tested. The level of antigen detected by MoAb 345.134S was unchanged in the presence of interferon but was decreased by puromycin exposure. The opposite was true for cell-dependent lysis of cultured human cells. (32 Refs)

22. T-CELL CHRONIC LYMPHOCYTIC LEUKEMIA: REPORT OF A CASE STUDIED WITH MONOCLONAL ANTIBODY.

Aisenberg AC, Wilkes BM, Harris NL, Koh HK
Massachusetts General Hosp., Boston, MA, 02114
Am J Med; 72(4):695-699 1982

A previously healthy 74-yr-old woman presented with T-cell chronic lymphocytic leukemia, lymphadenopathy, hepatosplenomegaly and a mediastinal mass. The circulating lymphocytes were small to medium in size (some with convoluted nuclei) and E rosette-positive; they could be assigned to the inducer-helper subset of T cells with the aid of monoclonal antisera. These cells reacted with OKT3, which detects peripheral T cells; OKT4, which detects the inducer-helper subset of T cells; and OKT11, which detects the sheep cell receptor. It is noteworthy that they were also positive for the Ia-like antigen found on T cells only after activation. Microscopic examination of a lymph node biopsy specimen revealed a diffuse pattern of pleomorphic large cells characteristic of the T-cell lymphomas and lymphocytic leukemias reported from Japan. However, the lymph node cells lacked the T-cell differentiation antigens present on the circulating lymphocytes. The findings of this case provide insight into the pathogenesis of this unusual disorder and are relevant to our understanding of the spectrum of surface antigens in the more common malignant lymphomas. (Author abstract) (34 Refs)

23. ACUTE LEUKEMIA WITH BURKITT'S LYMPHOMA CELLS IN TWO JAPANESE CHILDREN: CLINICAL MANIFESTATIONS AND CELL SURFACE MARKERS.

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Rinsho Ketsueki; 22(12):1962-1970 1981

Two cases of B-cell acute lymphoblastic leukemia (B-cell ALL) that showed cytological characteristics of Burkitt's lymphoma cells are reported. A 3 yr 5 mo old boy complained of vomiting, abdominal pain, fever, and had hyperuricemia. An extensive infiltration of peroxidase negative lymphoblastic cells was noted and the patient was diagnosed for ALL. Blast cells showed basophilic staining with several vacuoles on Wright-Giemsa staining. Surface immunoglobulin of IgM was detected in 84% of blast cells. Positive reactions against anti-B antigen (Ia-like antigen) serum (100%) and anti-common ALL antigen serum (38%) were noted, and the disease was determined to be B-cell ALL. Treatment with prednisolone and vincristine was initiated. Despite a transient cardiac arrest due to hyperkalemia, a complete remission was seen. Four wk later, however, the patient developed meningeal and testicular leukemia and refractory hematological relapse. The patient did not respond to further treatment and expired in 5.5 mo. A 3 yr 3 mo old boy complained of headache, abdominal pain, and pain in the right thigh. A massive infiltration of bone marrow by blast cells with morphological features similar to those in the first patient was observed. Cell surface analysis led to diagnosis of B-cell ALL. IgM was detected in 100% of blast cells, and positive reaction against the same antigens as in the first patient were observed. Meningeal leukemia also occurred. Prednisolone and vincristine treatment was discontinued due to ileo-ileal interssusception followed by diffuse peritonitis on day 1 of therapy. In 3 wk, a complete remission was seen. In 5 wk, however, refractory hematological relapse developed and the patient died of pneumonia after 3.5 mo. Both patients showed a high rate of surface Ig appearance, negative RBC antibody complement rosette, positive B-antigen (Ia-like), and weakly positive common ALL antigen. These observations suggest that B-cell ALL may have a pathogenesis similar to Burkitt's lymphoma. (31 Refs) (In JPN)

24. IMMUNOLOGIC CHARACTERIZATION OF A HELPER T-CELL LYMPHOMA.

Gramatzki M, Dolan MF, Fauci AS, Maples JA, Bonnard GD, Strong DM
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Blood; 59(4):702-70[illegible] 1982

The lymphocytes of a patient with a T-cell non-Hodgkin's lymphoma with peripheral blood involvement and polyclonal hypergammaglobulinemia were characterized in terms of surface markers and immunologic functions. Using the fluorescence-activated cell sorter and employing various monoclonal antibodies against T-cell surface antigens, it was shown that almost all of the patient's peripheral blood lymphocytes were positive for OKT4 and 9.3, antibodies that recognize helper T-cell subset. The circulating lymphoma cells had typical characteristics for T cells; they formed spontaneous rosettes with sheep erythrocytes and stained with the pan T-cell antibodies 9.6 and 10.2, but did not react with other anti-T-cell monoclonal reagents such as OKT3, UCHT-1, and 3A1. The cells appeared to be mature by the fact that they did not stain with OKT6, and terminal deoxynucleotidyl transferase was undetectable. Functionally, they were able to provide 'help' for antibody production, and they could be stimulated to produce moderate amounts of interleukin-2, while unable to proliferate in response to mitogens. Morphologically, some of the lymphocytes showed a deeply cleaved nucleus. (Author abstract) (53 Refs)

25. ANALYSIS OF ANTIGENIC DETERMINANTS ON HUMAN MONOCYTES AND MACROPHAGES.

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Blood; 59(4):775-786 1982

Mo1, 2, 3, and 4, and Plt-1 are a series of five distinct antigens detected on the surface of human peripheral blood monocytes by mouse monoclonal antibodies. Mo2 and 3 are restricted to the monocyte-macrophage series, while Mo1, as previously reported, is also expressed by human granulocytes and null cells. Mo3, as distinguished from Mo1 and Mo2, is weakly expressed by virgin peripheral blood monocytes but becomes well expressed if monocytes are cultured overnight at 37 C. Mo4 is coexpressed by monocytes and platelets, while Plt-1 appears to be a platelet-specific antigen whose detection on monocytes reflects adherence of platelets to monocyte membranes. That Mo2-4 are true monocyte antigens is demonstrated by their resynthesis following protease treatment of monocytes (Mo1 expression is resistant to proteolytic digestion). During myeloid-monocyte differentiation, the Mo antigens are infrequently expressed by immature myeloid cells but are found at higher frequency on leukemic monocytic forms. Macrophages from cultured peripheral blood monocytes and HL-60 cells exposed to lymphokines or phorbol diester express Mo1-4, but noncirculating peritoneal macrophages lack Mo3. the Mo antigens are differentiation markers whose expression reflects membrane heterogeneity during myeloid-monocyte-macrophage maturation. (Author abstract) (36 Refs)

26. ABNORMAL HUMORAL IMMUNE RESPONSES IN PERIPHERAL BLOOD LYMPHOCYTE CULTURES OF BONE MARROW TRANSPLANT RECIPIENTS.

Pahwa SG, Pahwa RN, Friedrich W, O'Reilly R, Good RA
Immunobiology Section, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021

Proc Natl Acad Sci USA; 79(8,part1):2663-2667 1982

The present study was aimed at investigating recovery of humoral immunity in vitro after bone marrow transplantation in patients with acute leukemia and severe aplastic anemia. Hemolytic plaque assays were utilized to quantitate pokeweed mitogen-stimulated polyclonal immunoglobulin production and sheep erythrocyte antigen-specific antibody responses in cultures of peripheral blood mononuclear cells of 39 patients beginning at 1 mo, for variable periods up to a max of 4 yr after marrow transplantation. Three phases were identified: an early period of primary B cell dysfunction with concomitant immunoregulatory T cell abnormalities - ie, decreased helper and increased suppressor activities; an intermediate phase in which B cell dysfunction could be attributed in large measure to immunoregulatory T cell abnormalities; and a late phase of normal B and T lymphocyte functions. Patients with graft-vs-host disease differed from those without it in that they often did not manifest increased T cell suppressor activity in the early period, and they were noted to have prolonged and profound B and T cell abnormalities in the chronic phase of their disease. In selected patiens, simultaneous assessment of ratios of Leu-2 to Leu-3 antigens on T cells by monoclonal antibodies and of immunoregulatory T cell functions revealed a correlation between the two only late in the post-transplant period. These studies provide an insight into the ontogeny of B cell function in the post-transplant period and indicate that in certain situations phenotypic alterations in T cell subsets cannot reliably be used to predict abnormalities in their function in recipients of marrow transplantation. (Author abstract) (37 Refs)

27. ABSENCE OF MELANOMA SPECIFICITY IN THE REACTIVITY OF MELANOMA PATIENTS' SERA WITH CULTURED ALLOGENEIC MELANOMA CELL LINES.

Dent PB, Liao SK, McCulloch PB, Stone BR, Singal DP
Dept. Pediatrics, Ontario Cancer Treatment and Res. Foundation, Hamilton Clinic, Hamilton, Ontario, L8N 3Z5, Canada

Cancer; 49(10):2043-2048 1982

While patients with melanoma are known to produce antibodies against melanoma cells, the tumor specificity of these reactions has not been well documented. Using the sensitive mixed hemadsorption assay we have identified antibody against one or more of nine different cultured melanoma cell lines in only 9 of 48 patients with melanoma. Reactivity against melanoma cell lines was seen only in females, 9/27 vs 0/21 males. The strongest melanoma reactivity was seen in sera which also contained lymphocytotoxic antibody. The reactivity was not melanoma specific because it could be removed by absorption either with pooled platelets, nonmelanoma tumor cells or in two cases, by both. We conclude that the occurrence of specific antimelanoma antibodies against common or shared surface melanoma associated antigens is an uncommon event in melanoma patients not receiving specific active immunotherapy. The clinical significance of the observed reactivity and whether it is directed against cancer associated determinants, fetal antigens, or normal tissue or histocompatibility antigens requires further study. (Author abstract) (31 Refs)

28. PROTEIN A REACTIVITY OF LYMPHOCYTES FROM SOME PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA MEDIATED BY AN INTERACTION WITH THE F(AB')2 REGION OF SURFACE IMMUNOGLOBULIN.

Romagnani S, Giudizi MG, Biagiotti R, Almerigogna F, Del Prete GF, Maggi E, Ricci M
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Scand J Immunol; 15(3):287-295 1982

Peripheral blood lymphocytes (PBL) from 15 of 38 patients with chronic lymphocytic leukemia (CLL) were capable of forming rosettes with human erythrocytes coated with staphylococcal protein A (SpA-HRBC). PBL from seven patients also showed a marked proliferative response after stimulation with Staphylococcus aureus bacteria strain Cowan I (Cowan Staph). The SpA-rosetting of CLL cells was inhibited by incubation with F(ab')2 fragments of anti-immunoglobulin (Ig) antibodies. In addition, incubation with these fragments inhibited the proliferative response of leukemic B cells to Cowan Staph. The Cowan-Staph-induced proliferation of CLL cells was also impaired by the addition of normal human IgG and human IgG F(ab')2 fragments to the cultures, whereas non-immune rabbit IgG was not inhibitory. The inhibitory activity of human IgG F(ab')2 fragments was retained by a SpA-Sepharose column, and it was found in the material recovered from the same column by acid elution. These data indicate that an interaction between SpA and a structure located in the F(ab')2 region of surface Ig of different classes is responsible for either SpA-binding or the Cowan-Staph-induced proliferative response of PBL from some patients with CLL. (Author abstract) (24 Refs)

29. BINDING OF PEANUT AGGLUTININ TO NORMAL HUMAN LYMPHOCYTES AND TO LEUKEMIC CELLS.

Barzilay M, Rosenthal E, Kende G, Reisner Y, Sharon N, Ramot B
Dept. Biophysics, Weizmann Inst. Science, Rehovat 76100, Israel

Leuk Res; 6(1):123-125 1982

Binding of fluorescein isothiocyanate-peanut agglutinin (PNA) to peripheral blood mononuclear cells was determined for 220 leukemic patients seen during the last 5 yr [85 acute lymphocytic (ALL), 29 acute myelo-monocytic, 14 Burkitt's, 28 ALL in remission, 68 chronic lymphocytic leukemia (CLL)]. Lectin-positivity, defined as greater than 20% PNA-binding cells, was found in 45% of ALL patients, 48% of myeloid leukemia patients, and 71% of Burkitt's leukemia and lymphoma patients, but in only 11% of ALL patients in remission. All 24 normal controls tested had binding less than 2%. Unlike acute leukemia cells, many of which had high (greater than 80%) binding, only 9% of CLL had greater than 80% binding. There was no clear correlation between binding level and the expression of T or B cell surface marker (T ALL, pre-B ALL, B ALL, null ALL). Because there are a significant number of ALL patients whose mononuclear cells do not bind PNA, it does not appear that this lectin can aid in classification of leukemias. (12 Refs)

30. LYMPHOMATOID GRANULOMATOSIS. AN ANALYSIS OF CLINICAL AND IMMUNOLOGIC CHARACTERISTICS.

Sordillo PP, Epremian B, Koziner B, Lacher M, Lieberman P
1275 York Ave., New York, NY, 10021
Cancer; 49(10):2070-2076 1982

Six patients with lymphomatoid granulomatosis were studied. Two patients had eye involvement, a rare manifestation of this disease. Both had complete disappearance of disease in this area after radiation therapy. One patient presented with an autoimmune hemolytic anemia, which remitted completely with chemotherapy. The use of corticosteroids or chemotherapy was effective in bringing about a decrease in pulmonary infiltrates in all six patients, although the duration of response was limited. One patient did have a prolonged period of clinical remission, and died of an unrelated cause. Evidence of profound immunologic abnormalities was found in these patients by a variety of tests. The extensive immunologic dysfunction present in patients with lymphomatoid granulomatosis has not previously been described. Most strikingly, patients with lymphomatoid granulomatosis have a severe impairment in T-lymphocyte function, confirmed by their inability to react to common skin test antigens or dinitrochlorobenzene, decreased in vitro lymphocyte responsiveness to mitogens and antigens and changes in T-cell subset populations. This may account for the frequent development of malignant lymphomas in patients with this condition. (Author abstract) (24 Refs)

31. IMMUNOREGULATORY FACTORS DERIVED FROM HUMAN TUMORS. I. IMMUNOLOGIC AND BIOCHEMICAL CHARACTERIZATION OF FACTORS THAT SUPPRESS LYMPHOCYTE PROLIFERATIVE AND CYTOTOXIC RESPONSES IN VITRO.

Roth JA, Grimm EA, Gupta RK, Ames RS
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J Immunol; 128(5):1955-1962 1982

Immunoregulatory factors (IRF) that suppress normal human peripheral blood mononuclear cell (PBM) function can be extracted from a variety of fresh human tumors. Three molar potassium chloride extracts of 18 fresh human tumor specimens, including sarcomas, melanomas, and lung carcinomas, markedly inhibited 3H-leucine and 3H-thymidine incorporation by PBM in response to mitogens (phytohemagglutinin, concanavalin A, Pokeweed mitogen) and pooled mitomycin C-treated allogeneic PBM. Induction of human allospecific cell-mediated cytotoxicity was also inhibited. Extracts of human normal and fetal tissues were not inhibitory. IRF could be extracted from either cultured tumor cells or from spent culture media from a melanoma cell line grown in chemically defined, serum-free media, demonstrating IRF is a tumor product. Although IRF were extracted from three histologically distinct tumors, the extracts had several common characteristics. Preincubation of PBM with IRF followed by washing prevented inhibition of lectin-stimulated proliferation. Inhibiton was greatest when IRF were added immediately to cultures. IRF were heat-stable and resisted inactivation by papain, chymotrypsin, protease, and lipase; they could be partially inactivated by trypsin treatment. Inhibitory activity was removed from extracts by lentil lectin affinity chromatography and recovered by elution with 3% alpha-methyl-D-mannoside indicating the active moiety contained a carbohydrate. Inhibitory activity was also abolished by extreme acid or base conditions and treatment with 2-mercaptoethanol. These results demonstrate that factors produced by human tumors suppress a variety of cell-mediated immune responses. Factors from histologically different tumors possess similar biochemical and immunobiologic characteristics. (Author abstract) (46 Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

32. TUMOR MARKERS IN CARCINOMA AND PREMALIGNANT STATES OF THE STOMACH IN HUMANS.

Skinner JM, Whitehead R
Dept. Pathology, Flinders Univ. South Australia, Bedford Park 5042, Australia
Eur J Cancer Clin Oncol; 18(3):227-235 1982

Tissue sections taken from areas of carcinoma, areas of intestinal metaplasia in stomachs bearing carcinoma and areas of intestinal metaplasia in stomachs showing atrophic gastritis only were examined for eight markers: a tumor-derived colon-specific antigen (tCSA), carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), pregnancy-specific beta-glycoprotein 1 (SP1), human placental lactogen (HPL), human beta chorionic gonadotrophin (beta-HCG), transferrin (TF) and ferritin (FE). In terms of the number of markers demonstrated in each of the three categories, there is a close similarity between the cells of adenocarcinoma and cells of intestinal metaplasia in cases of cancer, but not to similar metaplastic cells in atrophic gastritis cases. In addition, it appears that the presence of tCSA and SP1 is closely linked to carcinoma, though only approx half of such cases contain these markers. It would also appear that there are two types of morphologically identical intestinal metaplasia, one related to cancer, the other not. No difference was found between so-called intestinal type and diffuse type carcinomas. (Author abstract) (28 Refs)

33. TESTICULAR TUMOR MARKERS.

Scardino PT
Dept. Urology, Baylor Coll. Medicine, Houston, TX
Cancer Bull; 34(1):9-16 1982

Historical background, frequency of elevated markers, source of markers, and value of the markers in care of patients with testicular tumors are reviewed. Current practice in treatment of testicular tumors includes determinations of the presence and quantity of human chorionic gonadotropin (hCG) and alpha-fetoprotein (aFP), which closely reflect the nature, extent, and activity of these tumors in the patients. The frequency of elevated markers in nonseminomas reflects the extent, or pathologic stage, of the tumor, but in seminomas the meaning of elevated levels is controversial. Serum marker levels are valuable in diagnosis, staging, and long-term monitoring, but prognostic value is uncertain. Other biochemical markers of testicular cancer have been identified, but none adds sufficient information to that from hCG to warrant use in routine assay. Lactate dehydrogenase is an inexpensive, useful nonspecific tumor marker. The use of hCG and aFP markers has increased the accuracy of diagnosis and staging, revolutionized understanding of tumor histology, and substantially improved monitoring ability. The value of serial measurements of both hCG and aFP before and after each phase of treatment of testicular tumor is emphasized. (26 Refs)

34. SERUM FERRITIN AS A THIRD MARKER IN GERM CELL TUMORS.

Grail A, Bates G, Ward AM, Jones WG, Hancock BW
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Eur J Cancer Clin Oncol; 18(3):261-269 1982

Serial measurements of serum ferritin have been assessed as an additional marker in a study of 12 patients with germ cell tumors. The standard markers, serum AFP and beta HCG, were also assessed serially. During treatment elevated levels of serum ferritin were detected in 10 patients, elevated AFP in 10 patients and elevated beta HCG in 6 patients. A poor prognosis was associated with persistently raised serum ferritin and either, or both, elevated AFP and beta HCG levels. Decreasing levels of serum ferritin indicated favorable response to treatment; rising values were associated with recurrence or dissemination of tumor. Even if serum ferritin cannot be classed specifically as a tumor product, it may be useful in the early detection of residual or recurrent tumor. (Author abstract) (20 Refs)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

35. PROSTACYCLIN IN PROSTATIC CANCER: A BETTER MARKER THAN BONE SCAN OR SERUM ACID PHOSPHATASE?

Khan O, Hensby CN, Williams G
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Br J Urol; 54(1):26-31 1982

Prostaglandins have been implicated in the development and spread of malignant tumors. Gas chromatography and mass spectrometry (GC-MS) analysis of prostaglandins in benign and malignant prostatic tissue showed that prostacyclin (PGI2), a prostanoid known to induce bone resorption, was the major component. PGI2 is hydrolysed to 6-oxo-PGF1alpha. Plasma levels of 6-oxo-PFG1alpha were measured as an index of PGI2 formation in patients with benign and malignant prostatic disease. The mean plasma 6-oxo- level in an age-matched control group was comparable to that of patients with benign prostatic hypertrophy. A significant elevation was found in patients with a TO carcinoma (p less than 0.05). Plasma 6-oxo- levels rise with advancing disease and the concentration varied with the degree of tumor differentiation. Plasma 6-oxo- levels were a more accurate monitor of disease progression than tartrate labile acid phosphatase in patients with M1 carcinoma. Persistently elevated levels were associated with a bad prognosis. (Author abstract) (29 Refs)

36. SERUM THYROGLOBULIN IN THE MANAGEMENT OF PATIENTS WITH THYROID CANCER.

Barsano CP, Skosey C, DeGroot LJ, Refetoff S
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Arch Intern Med; 142(4):763-767 1982

We have reviewed our experience with the management of patients with thyroid cancer to assess the potential benefits of employing the serum thyroglobulin assay in patient management programs and to determine the optimal conditions for this application. Serum thyroglobulin levels were found to be more reliable when obtained from hypothyroid patients. Levels of thyroglobulin greater than 10 ng/mL appeared to be abnormally elevated in both thyroidectomized patients prior to radioactive iodine therapy (Group 1) and in thyroidectomized patients after radioactive iodine therapy (Group 2). Elevated thyroglobulin levels were found to be useful indicators of the presence of metastatic disease, whereas normal thyroglobulin levels were reliable indicators of the absence of metastases. In Group 1 patients, elevated thyroglobulin levels reliably predicted the presence of important total body scan uptake. In Group 2 patients, normal thyroglobulin levels reliably predicted the absence of total body scan uptake. The serum thyroglobulin assay can substantially reduce the need for repetitive total body scanning in the follow-up of Group 2 patients with thyroid cancer. (Author abstract) (22 Refs)

37. CURRENT STATUS OF FECAL OCCULT BLOOD TESTING IN SCREENING FOR COLORECTAL CANCER.

Winawer SJ, Fleisher M, Baldwin M, Sherlock P
Dept. Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY
CA; 32(2):100-112 1982

Early diagnosis of colorectal cancer vastly improves survival rate; fecal occult blood testing has been used in the past but was thought to be clinically unreliable. The test was recently reintroduced as the guaic paper slide test. The guaic undergoes phenolic oxidation if Hb is present in the stool and hydrogen peroxide in the test reagent. Sufficient quantities of blood anywhere in the gastrointestinal tract can lead to a positive test. Results of several community screening programs and controlled trials are presented along with guidelines for use of the test. (18 Refs)

38. DIAGNOSTIC SIGNIFICANCE OF PREGNANCY-ASSOCIATED ALPHA2-GLYCOPROTEIN IN PATIENTS WITH OVARIAN CANCER.

Sawada M, Shimizu Y, Okudaira Y, Matsui Y, Nishiura H, Hayakawa K
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Gynecol Oncol; 13(2):229-236 1982

Pregnancy-associated alpha2-glycoprotein (alpha2-PAG) levels were measured in several kinds of samples by a modification of Laurell's electroimmunoassay using a rabbit anti-alpha2-PAG serum. Samples were sera obtained from healthy females (46 cases), patients with benign ovarian tumors (8 cases), patients with ovarian cancers (18 cases), nude mice bearing heterotransplanted human ovarian cancers (4 cases), and ascites and urine of cancer patients. Serum alpha2-PAG levels in patients with benign ovarian tumors were 3.8 +-3.2 U/ul and almost the same as those of controls (2.6 +-3.0 U/ul). However, serum alpha2-PAG levels were higher in patients with ovarian cancers (12.0 +-3.7 U/ul). alpha2-PAG was scarcely detected in ascites or urine obtained from cancer patients, and was not detected in sera of tumor-bearing nude mice, despite the high levels of alpha2-PAG in those of original patients. The reliability of alpha2-PAG as a tumor-associated marker in patients with ovarian cancer was reinforced by the comparison of the positive rates of the two parameters, alpha2-PAG and carcinoembryonic antigen (CEA). (Author abstract) (26 Refs)

39. SERUM BETA-2-MICROGLOBULIN IN MULTIPLE MYELOMA: RELATION TO PRESENTING FEATURES AND CLINICAL STATUS.

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Service de consultation de Rhumatologie Sociale, Centre Gui-de-Chauliac, Hopital Saint-Eloi, 34059 Montpellier Cedex, France
Eur J Cancer Clin Oncol; 18(1):59-66 1982

Serum beta-2-microglobulin (B2m) levels were measured in 78 patients with multiple myeloma (MM) and were compared with values for normal individuals and patients with benign monoclonal gammopathies (BMG). Serum B2m levels and values corrected for renal function were significantly higher in patients with MM at time of diagnosis than in normal individuals (p less than 0.001) and were highly correlated with the total body burden of myeloma cells as derived from the staging system of Durie and Salmon. However there were no significant differences between values for BMG and low-mass MM. For patients evaluated following induction chemotherapy, there was also a clear correlation between serum B2m levels and the magnitude of tumor regression or progression (p less than 0.05). During the plateau-phase, serum B2m levels remained very stable and highly correlated with the residual tumor mass (p less than 0.001). It was concluded that (1) B2m was not a reliable marker to distinguish between BMG and low-mass MM and (2) B2m was a valuable marker for assessing initial tumor mass of patients with MM and response to chemotherapy (especially the plateau-phase), above all in patients with urine or low-serum monoclonal component levels. (Author abstract) (33 Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

40. INFLUENCE OF AGE, SEX AND CANCER ON THE ACTIVITIES OF GAMMA-GLUTAMYL TRANSPEPTIDASE AND OF DIPEPTIDYL AMINOPEPTIDASE IV IN RAT TISSUES.

Fujiwara K, Katyal SL, Lombardi B
Faculty Pharmaceutical Sciences, Nagasaki Univ., Bunkyo-machi 1-14, Nagasaki 852, Japan
Enzyme; 27(2):114-118 1982

Gamma-glutamyl transpeptidase (GTP; EC 2.3.2.2) is an enzyme known to show activity changes during development and carcinogenesis. Its activity was measured in the livers and lungs of female and male rats of different ages, in Morris hepatomas and in experimentally induced pancreatic carcinomas. For comparison purposes, the activity of another peptidase, dipeptidyl aminopeptidase IV (DPAP; EC 3.4.14.1), was assayed in the same tissues. GTP activity was high in fetal liver and hepatomas, but low in adult rat liver, with a marked sex difference, 3x higher in the female than in the male. In the pancreas, however, the activity of the enzyme was high in the adult but low in the fetus and in pancreatic carcinoma. There were no marked developmental changes or sex differences in pulmonary GTP activities. DPAP levels were low in fetal and neonatal liver and lung, they increased rapidly after birth and showed no sex differences in the adult. In Morris hepatomas and in pancreatic tumors the activity of DPAP was significantly lower than in normal adult liver and pancreas. These results suggest that measurements of GTP (and, to a lesser extent, DPAP) are remarkably suitable for the study of neoplastic cells and tissues. (Author abstract) (19 Refs)

41. DETECTION OF GAMMA GLUTAMYL TRANSPEPTIDASE IN THE LIVERS OF GERMFREE AND CONVENTIONAL RATS.

Pollard M, Luckert PH, Adams RA
Lobund Lab., Univ. Notre Dame, Notre Dame, IN, 46556
Lab Anim Sci; 32(2):147-149 1982

Germfree and conventional rats, 1-41 mo of age, were examined for gamma glutamyl transpeptidase in frozen sections prepared from their livers. This histochemical marker has been associated with early changes which develop following exposure to known carcinogenic agents. Positive gamma glutamyl transpeptidase markers were detected in 86% of germfree rats over 4 mo of age, and the gamma glutamyl transpeptidase foci were larger and more numerous as the animals aged, and the foci were prominent in rats with hepatic tumors. Gamma glutamyl transpeptidase foci were observed in 96% of livers from conventional rats at 11-20 mo of age. The agents responsible for induction of the gamma glutamyl transpeptidase foci in the liver were not identified. (Author abstract) (22 Refs)

42. MULTIPLE FORMS AND INHIBITORS OF URIDINE-CYTIDINE KINASE IN NEOPLASTIC CELLS.

Ahmed NK
Div. Biochemical and Clinical Pharmacology, St. Jude Children's Res. Hosp., Memphis, TN
Int J Biochem; 14(4):259-262 1982

Two isozymes of uridine-cytidine kinase, a rate-limiting enzyme in the salvage pathway for pyrimidine nucleotide biosysnthesis, were demonstrated in both mouse L1210 ascites leukemia and human malignant lymphoma cells by isoelectric focusing and Sepharose 6B column chromatography. Eleven compounds were tested in vitro for their ability to inhibit the uridine-cytidine kinase-catalyzed phosphorylation of uridine by ATP in kinase preparations from L1210 and human 6410 leukemia cells. The compounds tested were: 5-iodouridine, 5'-iodo-5'deoxyuridine, 5-bromouridine, 5-chlorouridine, 5-cyanouridine, 6-aminocytidine, 4-thiouridine, 5'-azido-5'-deoxycytidine, 5'-azido-5'-deoxyuridine, 5'-O-nitrouridine, and 5'-O-nitrofluorouridine. The last four compounds were effective inhibitors of the enzyme from both cell types. While various compounds are known to inhibit the de novo pathway for uridine monophosphate (UMP), none have been available as inhibitors of the salvage pathway or of uridine-cytidine kinase specifically. The 5'-azido and 5'-O-nitro analogs may have chemotherapeutic potential either administered singly or in combination with inhibitors of the de novo pathway to UMP. (14 Refs)

43. A HUMAN PLASMA CELL LINE: INDUCTION AND CHARACTERIZATION.

Miller CH, Carbonell A, Peng R, Paglieroni T, MacKenzie MR
Dept. Pathology, Sch. Medicine, Univ. California, MS-1, Room 3453, Davis, CA, 95616
Cancer; 49(10):2091-2096 1982

A stable line of IgG K producing human plasma cells was established from a myelomatous human bone marrow using conditioned media from a rapidly metabolizing lymphoblast line, RPMI 4098. Growth in RPMI 1640 (15% fetal calf serum) at 6% CO2 promoted a 62-hr doubling time with a preferred cell concentration of 1 x 10(6)/mL. Surface marker studies showed: no receptors for sheep erythrocytes, no surface immunoglobulins, variable number of cells bearing complement receptors and 83% bearing Fc receptors. Although transmission electron micrographs demonstrated a poorly developed endoplasmic reticulum, radioimmunoassay showed 23 ng IgG

and 28.7 ng Kappa were produced by 1 x 10(6) cells in 72 hr. Further, the cells are lipase, esterase and Epstein-Barr nuclear antigen negative. ASG banding showed a total chromosome number that varied from 46-49. Since the number of human plasma cell lines is limited, it is felt that this line will augment the immunobiological study of human myeloma. (Author abstract) (16 Refs)

44. TRANSFERRIN RECEPTORS IN TRANSFORMATION AND DIFFERENTIATION.

Yeh CJ, Faulk WP

Blond McIndoe Centre for Transplantation Biology, Queen Victoria Hosp., East Grinstead, Sussex RH19 3DZ, England

Protides Biol Fluid Proc Colloq; 29:451-454 1981

Human promyelocytic leukemia HL-60 cells, Burkitt's lymphoma Daudi cells, and myelogenous leukemia K562 cells were grown with 1.25% dimethylsulfoxide (DMSO), 0.1% sodium n-butyrate (SnB), or 1 x 10(-6) retinoic acid (RA) for 4 days at 37 C, and transferrin receptors and growth were examined. HL-60 cells originally consisted of myeloblasts and promyelocytes and differentiated to metamyelocytes and banded neutrophils following induction; Daudi and K562 cells were unchanged. The indirect immunofluorescence test revealed that all three cell lines were strongly reactive for transferrin receptors, but HL-60 cells were weakly reactive after culture with DMSO, SnB, or RA; Daudi and K562 cells remained strongly reactive. Growth of HL-60 cells was strongly inhibited by all three agents, Daudi cells by SnB, and K562 cells by RA; K562 cells were barely affected by SnB. These findings indicate a role for transferrin receptors in differentiation and transformation: loss of receptor activity may be interpreted as being an index of change from immature to mature or from malignant to normal. (18 Refs)

45. ENHANCED BINDING OF RETINOIC ACID TO ITS CELLULAR BINDING PROTEIN IN LEWIS LUNG TUMOR CYTOSOL BY ALKALINE PHOSPHATASE TREATMENT.

Gmeiner B, Zerlauth G

Institut fur Krebsforschung, Universitat Wien, Borschkegasse 8a, A-1090 Wien, Austria

Hoppe Seylers Z Physiol Chem; 363(3):337-340 1982

It is suggested that the action of retinoids is mediated by specific binding proteins. Such proteins for retinol and retinoic acid were isolated and characterized from several tissues. Retinoids might act in a manner similar to that known for steroid hormones. There is some evidence that the activity of steroid hormone receptors is influenced by phosphorylating-dephosphorylating processes. Here we report the influence of alkaline phosphatase on the specific binding of retinoic acid to Lewis lung tumor cytosol. (Author abstract) (15 Refs)

46. EVIDENCE FOR A NOVEL CIRCULATING ALPHA1 PROTEIN IN TUMOR-BEARING RATS. DIFFERENTIATION FROM ACUTE PHASE ALPHA1 PROTEINS AND FROM ALPHA1 FETOPROTEIN.

Herve F, Urios P, Grigorova AM, Cittanova N, Rondeau Y, Engler R, Broadhead G, Neish W

Equipe de Recherche No. 239, Centre National de la Recherche Scientifique, Universite Paris V., Paris, France

Biochem Biophys Res Commun; 105(3):861-868 1982

The isolation of a novel alpha1 protein (AP) from an experimental RD/3 rat sarcoma is described, and evidence that it is molecularly distinct from both acute phase AP and alphafetoprotein is presented. This new protein component may be linked to the development of the RD/3 tumor and may correspond to a tumoral protein. The presence of this protein may play a role in the modification of the transport properties of animals bearing an RD/3 tumor. (14 Refs)

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. SERIAL CARCINOEMBRYONIC ANTIGEN (CEA) IN METASTATIC BREAST CANCER (MBC) (MEETING ABSTRACT)

Mughal A, Hortobagyi G, Fritsche H, Buzdar A, Yap H, Blumenschein G, Swanson D
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-315 1982

One hundred sixty-seven patients (pts) with MBC were treated with combination chemotherapy including 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). All pts had plasma CEA determinations performed before FAC and serially thereafter. CEA levels were measured by a triple isotope, double antibody radioimmunoassay. The median follow-up was 15 months. Eighty-four pts had abnormal initial CEA values greater than 6 ng/ml (greater than 10 ng/ml for smokers). Forty-seven of 84 (56%) pts had complete response (CR)+ partial response (PR). All responding pts had gradual decrease in CEA levels. Response and remission duration (RD) were

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similar in patients with normal and abnormal CEA value. Nine patients had a rise in CEA level during initial 8 weeks of therapy. Repeat CEA level in 4 weeks decreased and all patients had clinical response. Pts in whom elevated pretreatment CEA levels returned to normal during therapy had longer RD (22 months) than responding pts in whom CEA did not become normal (8 months). Two consecutive CEA changes in the same direction correlated with response in 68 of 71 (95.7%) pts. Thirty-five of 38 pts who had progressive disease evidenced increasing CEA levels. Serial CEA level provided a lead time of 1 to 13 months (median 3 months) before clinical relapse was detected in 63% of pts. Two consecutive rising CEA values correlated with progression in 91.4% of pts. CEA is a useful marker for monitoring the clinical course of MBC. Early false rise in CEA level may occur with chemotherapy. Its use for early detection of progressive disease or as an additional criterion of response to systemic therapy makes it a valuable biologic marker. (no Refs)

2. CEA IN OVARIAN CANCER (MEETING ABSTRACT)

Malkin A, Kellen JA, Malkin DG, Sturgeon JF, Dombo AJ, Reid JG, McCabe EM
Sunnybrook Medical Centre, Toronto, M4N 3M5, Canada
Proc Am Soc Clin Oncol; 1:C-30 1982

The prognostic value of sequential carcinoembryonic antigen (CEA) tests was evaluated in 325 patients with ovarian cancer participating in a clinical trial. The initial CEA was determined within one to three months following surgery and at least four tests extending over six months were performed serially on all patients. We had established previously that CEA estimations are prognostic of survival independent of stage. In the present study, we tried to determine whether sequential CEA estimations are prognostic of recurrence and survival independent of the classical prognostic factors - stage, histopathologic differentiation and amount of residual disease following surgery. The sequential estimations were categorized as to whether the CEA levels were persistently abnormal, normal, rising, falling or variable. Using a log rank analysis, we found that sequential CEA estimations per se are prognostic of recurrence and survival and, when corrected for stage, tumor differentiation and residual disease following surgery remained prognostic of both recurrence and survival. Whether the persistent elevation of CEA reflects the presence of residual disease undetectable by other means or identifies a particularly malignant phenotype remains to be determined. (no Refs)

3. CARCINOEMBRYONIC ANTIGEN (CEA) DETECTION IN LUNG CARCINOMA IN GREECE.

Simos A, Kotsovoulou V, Papamichail C, Kontonasiou E, Apostolopoulou P, Toubis M, Anagnostides C, Assikis J, Coutoulides C
Chest Hosp., Athens, Greece
Excerpta Med Int Congr Ser; 558:237-243 1982

Role of carcinoembryonic antigen (CEA) assays in the clinical management, diagnosis, and therapeutic monitoring of lung carcinoma (LC) was studied in 83 patients (69 males, 14 females, av age 68.4 yr) with LC, and the relationship between plasma CEA levels and the stage of tumor spread and its degree of structural differentiation was examined. Seventy patients were heavy smokers. Controls included 17 patients with pulmonary obstructive disease and pulmonary tuberculosis. Histological classification of LC patients included: 39 squamous-cell, 26 adeno-, 13 small-cell, 3 undifferentiated, and 1 large-cell carcinoma. Serum CEA levels were 50 nanog (ng)/ml or greater in 25 patients, in 58 patients levels were less than 50 ng/ml. No clear association between CEA levels and the histological type of carcinoma was observed. Among 33 patients who presented as pleurisy of unknown origin, the 16 with LC included: 6 squamous-cell, 4 adeno-, 3 small-cell, and 3 undifferentiated carcinoma. In 13 out of these 16 LC patients, CEA levels in pleural fluid were found to be greater than the corresponding serum CEA levels. In 12/16 patients CEA levels were 50 ng/ml or greater. In two patients the serum CEA levels were within normal limits although the pleural fluid levels were 50 ng/ml or greater. All 17 controls had CEA levels below 10 ng/ml in both the serum and pleural fluid. Results indicated that little or no association exists between raised CEA levels and the histological type of cancer and that measurement of CEA activity in the pleural fluid of patients suffering from pleurisy of unknown origin may be a useful adjunct for the detection of malignant effusions. (10 Refs)

4. RADIOIMMUNOASAY OF ALPHA-FETOPROTEIN WITH POLYCLONAL AND MONOCLONAL ANTIBODIES.

Ruoslahti E, Uotila M, Engvall E
La Jolla Cancer Res. Foundation, La Jolla, CA, 92037
Methods Enzymol; 84:3-19 1982

Purification of alpha-fetoprotein (AFP) and radioimmunoassay of AFP are described. Measurement of AFP is usually conducted with radioimmunoassay capable of measuring several nanograms of AFP/ml in biological fluids. Because availability of purified AFP is a limiting factor for application the AFP assay, methods available for the preparation of standard AFP are described. Production of monoclonal antibodies to human AFP and the partial characterization of a highly sensitive radioimmunoassay utilizing such antibodies are reported. (29 Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

5. LACK OF VALUE OF RADIOIMMUNOASSAY FOR PROSTATIC ACID PHOSPHATASE AS A SCREENING TEST FOR EARLY PROSTATE CANCER (MEETING ABSTRACT)

Fleischmann J, Catalona WJ, Fair WR, Heston WD
No affiliation given
77th Annual Meeting of the American Urological Association, Inc; May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

There is controversy concerning the use of radioimmunoassays (RIA) for prostatic acid phosphatase (PAP) as a screening test for early prostate cancer. In a prospective study in which acid phosphatase was assayed routinely by RIA and an enzymatic method in 285 patients admitted to the Barnes Hospital Urology service, we found elevations of PAP by RIA in 16 patients who had no clinical evidence of prostate cancer. Six of these patients also had elevated serum acid phosphatases by the enzymatic determination. The 16 patients ranged in age between 62 and 83 years. All had bladder outlet obstructive symptoms requiring prostatectomy (5 open, 11 TUR). The prostatic acid phosphatase determinations were performed using the Malinckrodt RIA QUANT-PAP TEST KIT. Enzymatic acid phosphatase determinations utilized the thymolphthalein monophosphate substrate. Pathologic sections of the sur-

gical specimens were performed in the routine fashion; step sectioning was not performed. Carcinoma was found in none of the 16 prostatectomy specimens. In follow-up office examination, no patient has developed clinical evidence of prostate cancer (one died from an unrelated myocardial infarction). (no Refs)

6. CLINICAL USEFULNESS OF THE CREATINE KINASE BB ISOENZYME IN PROSTATIC CANCER (MEETING ABSTRACT)

Fritsche HA, Von Eschenbach A, Wertlake SE, Geltner AM
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

The creatine kinase BB isoenzyme (CK-BB) was evaluated for use as a tumor marker in patients with prostatic cancer. A radioimmunoassay procedure was used to determine the level of CK-BB in the circulation of these patients. A standard electrophoretic method was used to confirm the presence of the BB isoenzyme for those samples in which the radioimmunoassay procedure gave an elevated value. Most of the cancer patients had stage C or D adenocarcinoma of the prostate. Approximately one-half of the patients were undergoing therapy when they were entered into the study and the remainder of the patients were either in remission or had not yet received therapy for recurrence of their disease. One hundred and seventy serum samples were obtained from 33 patients during the follow-up period, and these were assayed for both CK-BB and prostatic acid phosphatase (PACP). In 16 of 33 patients, both the CK-BB and PACP values reflected progressive disease or response of the patient to therapy in a parallel manner. In seven patients who showed no clinical evidence of disease, serial values for both the CK-BB and PACP remained constant within normal limits. Serial CK-BB values indicated disease recurrence in four of 33 patients in which PACP values were normal and serial PACP values indicated disease recurrence in six of 33 patients in which the CK-BB values remained normal. (no Refs)

7. SERUM-SIALYLTRANSFERASE ACTIVITY IN CANCER PATIENTS.

Berge PG, Schriewer WH, Wust G
(c/o Schriewer), Med. Univ.-Klinik, Domagkstr. 3, D-4400 Munster, W. Germany
Klin Wochenschr; 60(9):445-449 1982

Serum-sialyltransferase activity was measured in serum samples of 116 patients with malignant tumors of various origins and different clinical stages using asialo-fetuin as the acceptor and cytidine-5'-mono-phospho[14C]sialic acid as the donor. Only patients with metastatic tumors had significantly elevated serum-sialyltransferase levels. Increased enzyme activity was also associated with rheumatoid arthritis and with acute hepatitis, whereas no significant alteration of enzyme activity was observed in cystic fibrosis patients. In a group of tumor patients, various additional tumor markers were determined (carcinoembryonic antigen, alkaline phosphatase: Regan isoenzyme, creatine kinase: BB-isoenzyme, lactate dehydrogenase: isoenzyme 5) and the data compared to the clinical diagnoses. The sensitivity and specificity of serum-sialyltransferase as a tumor marker is assessed. (Author abstract) (28 Refs)

8. IMMUNOCYTOCHEMICAL METHOD FOR THE DETECTION OF TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE IN ACUTE LEUKEMIA.

Ho AD, Helmstadter V, Hunstein W
Med. Univ.-Poliklinik, Hospitalstr. 3, D-6900 Heidelberg, W. Germany
Klin Wochenschr; 60(9):451-455 1982

Terminal deoxynucleotidyl transferase (TdT) has become an important marker for the classification of acute leukemias. Originally detected by a biochemical assay, the presence of this enzyme in leukemia can now be detected by making use of a highly specific antibody and by applying the immunofluorescence method. In this study, an attempt was made to apply the unlabeled peroxidase-antiperoxidase (PAP) technique for the examination of TDT positive cells. We have optimized this method and have compared the different assays - biochemical, immunofluorescence, and immunocytochemical (PAP) - in 10 patients with acute leukemia. The results obtained from all three methods are in accordance with one another, but the PAP method is a further simplification for the detection of TdT in the routine diagnosis of acute leukemias. (Author abstract) (13 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

9. ESTROGEN RECEPTOR ASSAY ON BREAST CANCER MICROSAMPLES. IMPLICATIONS OF PERCENT CARCINOMA ESTIMATION.

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Cancer; 49(11):2383-2388 1982

Forty-milligram strips of malignant breast tissue were divided longitudinally into 20-mg microsamples. Soluble protein concentration was determined for one-half, and histologic evaluation for viable carcinoma content was made on its sister half. The correlation coefficient for 88 such comparisons was 0.330. This suggests that estrogen receptor (ER) assays that do not take into account the actual amount of carcinoma present in the sample may not permit reliable stratification of ER data. Using this technique, ER values obtained for 129 breast tumor microsamples were adjusted to reflect carcinoma content. A comparison of ER values before and after such adjustment revealed that the relative status of 73% was not significantly changed. The ER status of 27%, however, was changed sufficiently to be of potential clinical significance. (Author abstract) (19 Refs)

10. OPTIMIZATION OF AN EXCHANGE ASSAY FOR THE MEASUREMENT OF SPECIFIC ESTROGEN BINDING SITES IN THE NUCLEUS OF NORMAL AND MALIGNANT HUMAN TISSUE (MEETING ABSTRACT)

Syne JS, Markaverich BM, Clark JH, Panko WB
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Proc Am Assoc Cancer Res; 23:943 1982

Our aim was to optimize the conditions of an exchange assay to measure the total concentration of estrogen receptors in the nuclei of cells from human breast tumors and myometrium.

Tissue homogenates were centrifuged through 1.2 M sucrose pads to separate crude chromatin from soluble and membranous fractions. The yield of DNA by this procedure was approximately 80%. Total binding sites were measured by incubating the sedimented pellets with tritiated estradiol at 30C for 60 minutes and then precipitating the receptor-steroid complexes with protamine sulfate. The advantages of the sucrose pad assay (SPA) are that: 1) it lowers the non-specific binding of [3H]-estradiol from about 80% to between 10 and 40% of the total binding measured, thereby circumventing one of the major problems encountered in most measurements of estrogen receptor levels in human breast tumors, 2) its reproducibility is well within acceptable limits with an intra-assay coefficient of variation of 16%, 3) it consistently measures a greater number of high affinity estrogen binding sites when compared to previously described assays carried out on crude nuclear pellets or high-ionic strength extracts of those pellets and 4) saturation analysis by the SPA provides the first compelling evidence for the presence of a second specific nuclear estrogen binding site other than the classical estrogen receptor in both human breast tumors and myometrium. (no Refs)

11. THE VALUE OF REPEATING STEROID RECEPTOR ANALYSES IN THE ENDOCRINE TREATMENT OF BREAST CANCER (MEETING ABSTRACT)

Stewart JF, King RJ, Steiner R, Hayward JL, Rubens RD
Imperial Cancer Research Fund Breast Cancer Unit, London SE1 9RT, England
Proc Am Soc Clin Oncol; 1:C-283 1982

One hundred and fifty-six patients with advanced breast cancer of known estrogen receptor (ER) and progesterone receptor (PgR) status treated by endocrine therapy were studied. Regarding a value for both ER and PgR as greater than or equal to 5 fmol/mg cytosol protein as positive, patients were divided into 4 phenotypic sub-groups:- ER+PgR+ (43%), ER+PgR- (26%), ER-PgR+ (8%) and ER-PgR- (23%). Responses to first endocrine therapy for each tumor phenotype were ER+PgR+ 50%, ER+PgR-27%, ER-PgR+ 27% and ER-PgR-6%. Four of 16 (25%) patients with ER+PgR+ tumors responded to subsequent endocrine therapy, but responses were not observed for 20 tumors of any other phenotype. With ER+PgR+ tumors, responses were seen in 20/30 (67%) patients when receptors were measured on tumor recurrence or on primary tumor immediately before endocrine therapy; but in only 11/32 (32%) when receptor analysis was performed on primary tumor and endocrine therapy was started only after failure of primary local therapy. In sequential analyses of receptors a change in ER phenotype occurred in 28/104 (27%) tumors, and in PgR phenotype in 12/42 (29%). These results demonstrated that repeat steroid receptor assays immediately before endocrine therapy improve the prediction of response to treatment. (no Refs)

12. DECREASED NOCTURNAL PLASMA MELATONIN PEAK IN PATIENTS WITH ESTROGEN RECEPTOR POSITIVE BREAST CANCER.

Tamarkin L, Danforth D, Lichter A, DeMoss E, Cohen M, Chabner B, Lippman M
NIH, Building 6, Room 136, Bethesda, MD, 20205
Science; 216(4549):1003-1005 1982

Plasma melatonin concentrations were determined over a period of 24 hr in 20 women with clinical Stage I or II breast cancer. In 10 of the patients, whose tumors were estrogen receptor positive, the nocturnal increase in plasma melatonin was much lower than that observed in 8 control subjects. Women with the lowest peak concentration of melatonin had tumors with the highest concentrations of estrogen receptors. A significant correlation was found between the peak plasma melatonin concentration and the tumor estrogen receptor concentration in 19 of the patients. These data suggest that low nocturnal melatonin concentrations may indicate the presence of estrogen receptor positive breast cancer and could conceivably have etiologic significance. (Author abstract) (18 Refs)

13. THE IMPORTANCE OF EARLY DIAGNOSIS IN PATIENTS WITH HEREDITARY MEDULLARY THYROID CARCINOMA.

Wells SA, Baylin SB, Leight GS, Dale JK, Dilley WG, Farndon JR
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Ann Surg; 195(5):595-599 1982

Ninety-two patients from 12 kindreds with hereditary medullary thyroid carcinoma (MTC) were evaluated. We sought to determine if the stimulated plasma calcitonin (CT) level at the time of diagnosis was of prognostic significance. The patients were divided into four groups according to their preoperative stimulated plasma CT levels (1) 250-1,000 pg/ml (n = 25); (2) 1,000-5,000 pg/ml (n = 36); (3) 5,000-10,000 pg/ml (n = 8); (4) greater than 10,000 pg/ml (n = 23). Compared between the four groups were several parameters, including incidence of regional lymph node metastases, incidence of residual MTC post-thyroidectomy (as indicated by increased (greater than 300 pg/ml) plasma CT levels after operation), incidence of distant metastases, and incidence of death. Also compared were the incidences of microscopic or gross MTC in thyroidectomy specimens. The incidence of regional lymph node involvement ranged from a minimum of one (4%) of 25 patients in Group 1 to 13 (57%) of 23 patients in Group 4. Similarly, plasma CT levels were elevated in only one (4%) of 25 patients in Group 1 compared to 14 (61%) of 23 patients in Group 4. There was no evidence of distant metastases or death in the patients in Groups 1, 2, or 3. In the 23 patients in Group 4, however, four (17.4%) had distant metastases and two (8.7%) died of disease during the period of observation. Of the 25 patients in Group 1, MTC was evident only by microscopic examination in 14 (56%). Eleven (44%) of the patients in Group 1 had macroscopically evident medullary thyroid carcinoma. This is in contrast with patients in Group 4 where all 23 had grossly evident MTC. These data indicate that the stimulated plasma CT level at the time of diagnosis is an excellent prognostic indicator of the extent of a disease in patients with hereditary MTC. Aggressive screening of kindred members at risk of critical importance for establishing the diagnosis and instituting therapy at a time when the neoplasm is confined to the thyroid gland. (Author abstract) (8 Refs)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

14. IN VITRO PRODUCTION OF TUMOR-RELATED HUMAN MONOCLONAL ANTIBODY AND ITS IMMUNOHISTOCHEMICAL SCREENING WITH AUTOLOGOUS TISSUE.

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Gan; 73(2):345-347 1982

The property of Epstein-Barr virus (EBV) to transform human B lymphocytes into lymphoblastoid cells secreting immunoglobulins was used to obtain human antibodies against human tumors. EBV was taken from the marmoset cell line B95-8. A virus stock was produced by culturing B95-8 cells for 7 days in a medium of RPMI-1640 supplemented with 20% heat inactivated fetal bovine serum, 100 Units/ml penicillin, and 100 ug/ml streptomycin, separating culture supernatants, and filtering through a Millipore filter. Regional lymph nodes were obtained at surgery from a 45-yr-old woman with Dukes' C moderately-differentiated adenocarcinoma of the rectum and from a 37-yr-old man with Borrmann's Type II signet ring cell carcinoma of the stomach. Single cell suspensions were prepared from the lymph nodes, resuspended in culture medium, and then mixed with virus stock. A 0.1 ml portion of the resulting mixture was distributed to 92-well tissue culture plates, cultured for 4 wk, and transferred to 24 other well tissue culture plates for 2 more wk of culturing. Culture supernatants were harvested and screened for the presence of antibody against autologous tumor tissue. In the case of rectal cancer, supernatants from 6/24 well positively stained the autologous tissue. The reaction products were located at the luminal surface of tumor cells, and the distribution was quite similar to that of carcinoembryonic antigen. In the case of gastric cancer, supernatants from 7/24 wells positively stained the autologous tissue. The results demonstrate that human antibodies against human tumors and normal tissues can be produced by EBV transformation of lymphocytes, suggesting that there is potential clinical application of this technique for treating tumors and that lymphocytes producing autoantibodies against normal tissues could be easily cultured from the lymph nodes adjacent to tumors. (6 Refs)

15. MONOCLONAL ANTIBODY BA-1 DOES NOT BIND TO HEMATOPOIETIC PRECURSOR CELLS.

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Blood; 59(5):1029-1035 1982

Monoclonal antibody BA-1 binds to B-lymphocytes, to cells from most cases of non-T acute lymphoblastic leukemia (ALL), and weakly to neutrophils. To determine whether BA-1 also reacts with hematopoietic progenitor cells (HPC), we studied the effect of removal of BA-1+ cells from human bone marrow on the proliferation in vitro of the trilineage precursor cell CFU-GEMM, and of the committed progenitor cells of granulopoiesis (CFU-C) and erythropoiesis (BFU-E/CFU-E). Complement-mediated cytotoxicity using BA-1 at concentrations far beyond those required to lyse BA-1+ bone marrow cells and ALL cells did not result in inhibition of colony formation in any of the assays. A rosette separation method, using ox red blood cells coated with BA-1, resulted in enrichment of HPC in the BA-1-depleted interface, whereas very few HPC were found in the BA-1-enriched pellet. Both methods indicate that BA-1 does not bind to HPC, although binding of the antibody to the lymphohematopoietic stem cell cannot be excluded yet. The high cytotoxic capacity of the IgM antibody BA-1, and the lack of reactivity with HPC, make the antibody particularly suitable for use in autologous bone marrow transplantation for patients with ALL. (Author abstract) (26 Refs)

16. PLATELET ASSOCIATED IGG IN PATIENTS WITH LYMPHOMA (MEETING ABSTRACT)

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Proc Am Soc Clin Oncol; 1:C-31 1982

Thrombocytopenia and platelet-associated IgG(PAIgG) have been described in association with Hodgkin's (HD) and non-Hodgkin's lymphoma (NHL). To estimate the incidence of PAIgG in patients (pts) with these disorders, 49 consecutive pts with HD or NHL seen at this Center were screened for PAIgG using a modification of the platelet radioactive antiglobulin test of Mueller-Eckhardt. Nine of 20 pts (45%) with HD and 9/29 pts (31%) with NHL had positive assays. Pts with HD and PAIgG tended to have lower platelet counts (PC) than those with HD and negative PAIgG. There appeared to be a higher incidence of thrombocytopenia during the course of treatment in pts with HD and PAIgG. All pts with HD and PAIgG had advanced stage and all were nodular sclerosing or mixed cellularity subtypes. In HD, PAIgG was not independently predictive of active disease (8/9 PAIgG positive and 7/11 PAIgG negative pts had active disease). PAIgG became negative, however, in 4 pts on treatment. In pts with NHL, PAIgG correlated with active disease and occurred exclusively in the poor prognostic categories. There was no difference in PC between PAIgG positive and negative pts with NHL. Hypergammaglobulinemia was not related to increased PAIgG. This study indicates an unrecognized high incidence of PAIgG with lymphoma. (no Refs)

17. CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITH IGM LAMBDA CYTOPLASMIC INCLUSIONS (CI) - A 'POST PRE-B CELL?' (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:1027 1982

The immunoglobulin (Ig) abnormalities of CLL cells arrested at varying stages of maturation provide potential insights into B cell differentiation. Although CLL cells with CI have been described, the nature of the Ig defect and stage of cell differentiation are unclear. We have extensively characterized cells containing CI from a patient with Rai Stage II CLL with hypogammaglobulinemia and severe recurrent infections. The cells were Ia positive, but surface staining with fluorescein-conjugated anti-Ig (SIg), initially and after culture to remove cytophilic antibodies, was much fainter than typical CLL. Moreover, unlike typical CLL cells, no class specific SIg could be identified in repeated experiments. In contrast, cytoplasmic staining revealed the inclusions to contain mu and lambda Ig. Unlike mu heavy chain disease, no mu component was present in the serum or urine, although a small monoclonal lambda component was identified in the urine. Ig production in vitro, determined by 3H leucine incorporation into Ig, assayed by co-precipitation with anti-Ig, was similar to typical CLL and was unaffected by pokeweed mitogen stimulation. Cells cultured in the presence of phorbol myristate acetate (PMA) had increased IgM lambda CI, but did not differentiate to diffuse plasma cell-

like cytoplasmic Ig as do normal B cells. These phorbol 12-myristate 13-acetate stimulated cells expressed globular IgM lambda SIg rather than the usual diffuse B cell SIg. (no Refs)

18. CLONAL EXCESS (CE) DETERMINATION BY CYTOFLUOROMETRIC ANALYSIS OF IMMUNOGLOBULIN LIGHT CHAIN EXPRESSION IN B-CELL NEOPLASIAS (MEETING ABSTRACT)

Gebhard DF, Koziner B
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Soc Clin Oncol; 1:C-738 1982

Cytofluorometric analysis of membrane immunoglobulin light chain expression was carried out in peripheral blood (PB) and/or bone marrow (BM) density separated monolayer cells to determine CE defined as (% kappa+ - % lambda+)/(% kappa+ + % lambda+) per discrete level of fluorescent intensity. Twenty normal controls and 53 patients with B-cell neoplasias, including 22 B-chronic lymphocytic leukemia (CLL), 6 hairy cell leukemias (HCL) and 25 follicular center cell leukemic lymphomas (FCCLL) were studied and compared to a concurrent battery of conventional surface markers (SM) including membrane immunoglobulin by fluorescence microscopy, sheep erythrocyte, mouse erythrocyte and complement rosettes. CE analysis was able to confirm SM results in 10/22 CLL, 6/6 HCL and 13/25 FCCLL. The remaining cases- where CE was evident by cytofluorometric analysis but not by conventional SM - were detected by either: a) analysis of fluorescence distribution where there were nearly equal numbers of kappa and lambda stained cells, or b) the increased sensitivity of flow cytometric analysis to determine weakly stained cells. Leukemic and normal cells were mixed at various dilutions to determine the maximum dilution that could yield an unequivocal determination of CE. For CLL and FCCLL the maximum dilutions were 1:10 and 1:20, respective of the characteristic levels of fluorescence intensity. Dilutions higher than these yielded CE values indistinguishable from normal, though the fluorescence profiles resembled the undiluted leukemic profile and were thus open to speculative interpretation. (1 Ref)

19. LYMPHOMA IN CARDIAC ALLOTRANSPLANT RECIPIENTS. CLINICAL AND HISTOLOGICAL FEATURES AND IMMUNOLOGICAL PHENOTYPE.

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Transplantation; 33(4):347-351 1982

To characterize further lymphomas which arise in chronically immunosuppressed allotransplant patients, we studied the clinical and histological features of seven cases of nonHodgkin's lymphoma and determined the immunological phenotype in four cases, which developed in a series of 182 patients who underwent cardiac transplantation at Stanford University Hospital. Clinical features which were correlated with the development of lymphoma included patient age, pretransplant diagnosis, and the number of transplants. All cases of non-Hodgkin's lymphoma presented as solitary or multiple localized extranodal lesions while none presented in lymph nodes. Extranodal sites of involvement included brain, lung, and soft tissues of the thigh at the site of antilymphocyte serum injections. Histologically, five of seven lymphomas were classified as high grade, large cell, immunoblastic and two of seven as intermediate grade, large noncleaved cell. The immunological phenotype of the neoplasm from four patients was determined by reaction with immunoglobulin light and heavy chain reagents and monoclonal antibodies to T cell and B cell antigens. All lymphomas from four patients which were tested stained for Ia antigen (HLA-DR) but did not stain for immunoglobulin or the T cell antigens detected in this study. (Author abstract) (33 Refs)

20. DEFICIENT HELPER T CELL ACTIVITY IN NON-HODGKIN'S LYMPHOMAS (MEETING ABSTRACT)

Silver BA, Bostick-Bruton FW, Young RC, Fisher RI
Medicine Branch, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:991 1982

The observations that lymphomas are more common 1) after organ transplantation and immunosuppressive therapy, and 2) in certain autoimmune diseases suggest that altered immunoregulation may play a role in lymphoma pathogenesis. Thus, we investigated regulatory T cell function in the peripheral blood in 13 untreated adult non-Hodgkin's lymphoma patients and 13 age and sex matched controls. Six patients had nodular lymphomas, 7 diffuse. Nine had B cell tumors. No known T cell tumors were studied. Control mononuclear leukocytes (MNL) had greater proliferative responses to pokeweed mitogen (PWM) than patient MNL. MNL were separated into T and non-T fractions by two sequential neuraminidase-E-rosette sedimentations. Non-T cells were unresponsive to PWM. Responses of normal and patient T cells were similar. When normal non-T and autologous irradiated (3000R) T cells were cocultured, the response exceeded the response of patient non-T and autologous irradiated T cocultures. When normal non-T cells were cocultured with patient irradiated T cells, their response was diminished. Moreover, when patient non-T cells were cocultured with normal irradiated T cells, their response was enhanced. Normal non-T cell responses were the same regardless of whether autologous or normal allogeneic irradiated T cells were used as helpers. These results suggest that peripheral blood T cells from patients with non-Hodgkin's lymphoma are deficient in helper capacity for non-T cell blastogenic response to PWM and that patient non-T cells may have a normal proliferative response in the presence of normal allogeneic (helper) T cells. Abnormal immunoregulatory cell function may be important in the pathogenesis of the non-Hodgkin's lymphomas. (no Refs)

21. PHENOTYPING HUMAN LEUKEMIC T-CELL LINES: ENZYME MARKERS, SURFACE ANTIGENS AND CYTOGENETICS.

Martin PJ, Giblett ER, Hansen JA
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Immunogenetics; 15(4):385-398 1982

We have compared phenotypic markers for a series of established human leukemic T-cell lines collected from different laboratories. Cell lines were tested first for genetic markers using polymorphic enzymes and then for expression of T lymphoid cell surface differentiation antigens using monoclonal antibodies. Chromosomal analysis was used as an additional method for identification of selected cell lines. On the basis of enzyme markers, it was possible to assign each of the cell lines examined to one of nine different groups. With two exceptions, surface antigen phenotypes for each of 12 cell lines were clearly distinctive. Thus, some groups of cell lines indistinguishable by enzyme markers could be further subdivided by surface antigen phenotyping. However, significant quantitative variation in expression of individual antigens was observed. In addition, surface antigen expression was not uniform in different subcultures of one cell line studied in detail. These results indicate that leukemic T-cell lines cannot be used generally as

simple models of surface antigen expression in normal T-cell differentiation. (Author abstract) (38 Refs)

22. SELECTIVE IMPAIRMENT OF SUPPRESSOR T CELL FUNCTION AFTER ADMINISTRATION OF CYCLOPHOSPHAMIDE (CY) (MEETING ABSTRACT)

Berd D, Danna V, Maguire H, Mastrangelo MJ
The Fox Chase Cancer Center, Philadelphia, PA, 19111
Proc Am Assoc Cancer Res; 23:1104 1982

Administration of CY to patients with metastatic cancer 3 d prior to immunization with antigen augments the delayed type hypersensitivity (DTH) response to that antigen. To explain this finding, we collected peripheral blood lymphocytes (PBL) from patients with metastatic melanoma before and after (1, 2, 3, 7, 14, and 21 d) CY 1000 mg/M2 IV. PBL were frozen, and all samples from a patient were thawed and tested on the same day. We performed PBL counts, analyzed the composition of PBL with a panel of fluoresceinated monoclonal antibodies and a cell sorter, measured their response to phytohemagglutinin (PHA) and pokeweed mitogen (PWM), and tested their ability to generate concanavalin A (Con A) suppressor cells. The PBL count decreased by a mean of 34.8% at 2 d and remained depressed through 21 d. There was no significant change in the relative proportions of B cells (Ig+), T cells (Leu 1+), or the helper-inducer (Leu 3+) or suppressor-cytotoxic (Leu 2+) subsets of T cells. In contrast, there was a change in the function of PBL after CY. Thus, 3 d and 7 d after CY, the ability to generate suppressor T cells was diminished, while the response to PHA and PWM, dependent on helper T cells, had recovered. This selective impairment of suppressor function could explain the immunopotentiating effect of CY in these patients. (1 Ref)

23. IMMUNOHISTOCHEMICAL ANALYSIS OF THE DISTRIBUTION OF LYMPHOCYTE SUBPOPULATIONS IN HODGKIN'S DISEASE.

Borowitz MJ, Croker BP, Metzgar RS
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Cancer Treat Rep; 66(4):667-674 1982

We studied the histologic distribution of lymphocyte subpopulations in Hodgkin's disease. Involved tissues from 15 patients were stained by an indirect immunoperoxidase procedure for a variety of lymphocyte surface antigens using monoclonal antibodies. In most cases, there were more T cells than B cells, and Reed-Sternberg cells were found in T-cell-rich areas. Except in lymphocyte-depleted Hodgkin's disease, helper-T antigen-positive (TH) cells greatly outnumbered cytotoxic-suppressor antigen-positive cells. Moreover, TH cells showed a preferential association with Reed-Sternberg cells. Lymphocytes surrounding Reed-Sternberg cells often expressed the transferrin receptor, a marker of cell activation. Our results do not support the hypothesis that the lymphocytes in Hodgkin's disease represent a cytotoxic T-cell response to neoplastic cells, except perhaps in the lymphocyte-depleted subtype. (Author abstract) (24 Refs)

24. IMPLICATIONS OF PERSISTENT T CELL ABNORMALITIES FOR THE ETIOLOGY OF HODGKIN'S DISEASE.

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Cancer Treat Rep; 66(4):681-687 1982

Untreated patients with Hodgkin's disease are known to have significant impairment of cellular immunity. Recent studies have demonstrated that effector T cells from these patients have increased sensitivity to the suppression mediated by two normal immunoregulatory cells, ie, suppressor monocytes and suppressor T cells. Thus, increased sensitivity to suppression may be a common cause of multiple abnormalities of cellular immunity. Patients achieving long-term disease-free survival after chemotherapy have also been studied. Although they are no longer anergic, they have persistent reductions in peripheral blood E rosettes and T cell proliferation. Increased sensitivity to suppressor monocytes and T cells also persists. These abnormalities do not appear to be caused by the treatment since they were not detected in diffuse histiocytic lymphoma patients surviving after similar chemotherapy. Immunologic studies in family members are required to determine whether these abnormalities are a permanent immunologic deficit acquired only with the development of Hodgkin's disease or an inherited characteristic that predisposes a patient to develop Hodgkin's disease. (Author abstract) (22 Refs)

25. DISTINGUISHING FEATURES OF THE IMMUNOLOGY OF HODGKIN'S DISEASE IN CHILDREN.

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Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer Treat Rep; 66(4):969-975 1982

Laboratory tests of immunologic function were done in 96 children with Hodgkin's disease, at diagnosis and during and after treatment. Over the same period of time, 29 age-matched control children were tested. The results presented in this report indicate that the immunology of childhood Hodgkin's disease has some features that distinguish it from the immunologic features of the disease in adults: (a) no progressive lymphopenia was found with advanced clinical stages; (b) peripheral blood T-lymphocyte counts were normal or high, and slight B lymphocytopenias were observed in children at all stages of the disease; (c) in spite of normal T-lymphocyte counts, a defective response to phytohemagglutinin stimulation was seen at diagnosis; and (d) recovery of the phytohemagglutinin response occurred with treatment and was related to modality of therapy and prognosis. (Author abstract) (18 Refs)

26. THE IMMUNOLOGIC CHARACTERIZATION OF 40 EXTRANODAL LYMPHOID INFILTRATES. USEFULNESS IN DISTINGUISHING BETWEEN BENIGN PSEUDOLYMPHOMA AND MALIGNANT LYMPHOMA.

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Cancer; 49(11):2321-2335 1982

In the studies described here, 40 extranodal lymphoid tumors obtained from 38 patients were evaluated by cell-marker analysis and the results correlated with the light microscopic features. These infiltrates were investigated for the percent composition of cells expressing Ia antigens, surface immunoglobulin (SIg), including K and lambda light chains, sheep erythrocyte (E) rosette formation, and acid a-naphthyl acetate esterase (ANAE) activity. Fifteen biopsy specimens consisted of variable proportions of benign T and polyclonal B cells; these 15 lesions had the histopathologic features of benign pseudolymphomas. The remaining biopsy specimens consisted almost entirely of B cells bearing monoclonal SIg (18 cases) or a great preponderance of T cells (5 cases) or non-B, non-T (null) cells (2 cases); these 25 lesions were classified histopathologically as

malignant lymphomas. Thus, the extranodal lymphoid infiltrates were divisible, according to their cell-marker characteristics, into two categories: lesions that are immunologically polyclonal and lesions that are immunologically monoclonal B-cell proliferations or consist of a great preponderance of T or null cells. In each case, polyclonality correlated with benign cytomorphologic features and monoclonality correlated with malignant histopathology. Cell-marker analysis appears to represent an important adjunct to light microscopy in distinguishing histologically problematic benign pseudolymphomas from malignant lymphomas that arise in the extranodal tissues. Cell marker analysis will undoubtedly provide insights into the histogenesis, natural history, and biologic behavior of the extranodal lymphoid neoplasms not attainable using light microscopy alone. (Author abstract) (32 Refs)

27. PEANUT AGGLUTININ: A MARKER FOR NORMAL AND LEUKAEMIC CELLS OF THE MONOCYTE LINEAGE.

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Clin Exp Immunol; 48(2):329-338 1982

The potential of peanut agglutinin (PNA) as a monocytic lineage marker and a diagnostic tool was investigated. Peripheral blood mononuclear cells (MNC) from normal adults, and 20 patients with acute non-lymphocytic leukemia (ANLL), as well as five human cell lines were analyzed for fluorescein isothiocyanate (FITC)-PNA binding using the fluorescence activated cell sorter (FACS). Monocytes and monoblasts, which were positive for non-specific esterase activity, bound FITC-PNA. In addition, FITC-PNA was bound by a population of cells not defined by cytochemical criteria which were probably precursors to monoblasts. The classical myeloid blast cell did not bind FITC-PNA. ANLL classification is discussed in the light of these results. FITC-PNA clearly binds to cells of the monocyte lineage, and has potential as an adjunct to current cytochemical and morphological criteria in classification. (Author abstract) (25 Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

28. CALCITONIN AND CARCINOEMBRYONIC ANTIGEN IN POORLY DIFFERENTIATED FOLLICULAR CARCINOMA.

Calmettes C, Caillou B, Moukhtar MS, Milhaud G, Gerard-Marchant R
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Cancer; 49(11):2342-2348 1982

Previous studies have shown that certain patients suffering from poorly differentiated follicular carcinoma (PDFC) of the thyroid had high levels of calcitonin (CT) and carcinoembryonic antigen (CEA) in the plasma. In this work, both CT and CEA were localized in tissue sections obtained at operation from patients suffering from PDFC. The results confirm the hypothesis that certain cases of PDFC are in fact CT-secreting tumors and represent another type of thyroid neoplasma. Patients suffering from PDFC should be screened using both CT and CEA assays. (Author abstract) (26 Refs)

29. CORRELATION OF THYMIDINE KINASE ACTIVITY, HISTOLOGY AND STEROID RECEPTORS IN PRIMARY BREAST CANCER (MEETING ABSTRACT)

Zhang HJ, Snover D, Kennedy BJ, Kiang DT
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Proc Am Soc Clin Oncol; 1:C-29 1982

Tumor steroid receptor content and differentiation correlate with the recurrence rate of primary breast cancer. For predicting prognosis, we investigated another biological marker, thymidine kinase activity (TK) by the method of Breitman, as well as estrogen receptor (ER) by the DCC method and progesterone receptor (PgR) by the sucrose gradient method. Results were correlated in 48 primary breast cancer tissues. No correlation was found between TK and PgR in 38 tumors. When tumors were divided into ER-poor (less than 3 fmol), medium (3-30 fmol), and rich (greater than 30 fmol) groups, a correlation of TK with ER was found in the first two groups. High TK activity occurred in 71% (10/14) of ER-poor tumors, while only in 18% (3/18) of ER-medium tumors. In the ER-rich group, 9 of 16 tumors also contained high TK, probably resulting from 'hormonal stimulation.' In 33 tumors, detailed histological grade was analyzed by the method of Bloom and Richardson, and no correlation with TK was found. This study suggests that (1) ER-poor primary breast tumors usually have high TK and (2) high TK also exists in some of the ER-rich tumors. The significance of TK as a prognostic factor for disease recurrence and for response to chemotherapy warrants further study. (no Refs)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

30. PURIFICATION AND CHARACTERIZATION OF PCA-1: A POSSIBLE MARKER FOR PROSTATIC CANCER (MEETING ABSTRACT)

Guevara JG, Chiocco EA, Von Eschenbach AC, Edwards JJ, Anderson NG
No affiliation given
77th Annual Meeting of the American Urological Association, Inc; May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Using two dimensional gel electrophoresis, a unique protein spot, designated PCA-1, has been identified in the urine of patients with adenocarcinoma of the prostate. This protein spot has not been found in urine samples from age-matched controls, patients with benign prostatic hyperplasia or other malignancies. This protein has been shown to be of prostatic origin and is being studied as a possible marker for prostatic cancer. The PCA-1 spot has been extracted from the two dimensional gels and three distinct proteins have been separated on a hydroxyl apatite column. The amino acid composition of these three proteins has been determined. Although these proteins have the same isoelectric point (pI) and similar molecular weights of 41,788, 42,875, and 43,393, their amino acid compositions are distinct. These proteins will be utilized in the development of immunoassays in order to facilitate the systemic evaluation of PCA-1 as a marker for prostatic cancer. (no Refs)

31. N-ACETYLNEURAMINIC ACID (NANA) AND PROGNOSIS IN MALIGNANT MELANOMA (MM) (MEETING ABSTRACT)

Silver HK, Murray RN, Karim KA, Salinas FA, Spinelli JJ
Cancer Control Agency of British Columbia, Vancouver, British Columbia V5Z 3J3, Canada
Proc Am Soc Clin Oncol; 1:C-7 1982

We have previously shown that serum NANA concentration can serve as a relatively sensitive monitor of tumor burden in a variety of neoplasms including MM. In this study we wished to determine the relationship of serum NANA to known prognostic factors for MM. Eligible MM patients (pts) had no evidence of residual disease at the time of serum sampling, have been followed for 2-5 yrs, and include 151 pts, with initial disease confined to the primary site (stage I) and 10 pts with regional lymphatic extension (stage II). A Cox proportional hazards model was used to identify significant independent predictors of disease free survival (DFI). Four of the 9 factors examined were not predictive: sex, primary site, tumor diameter, and stage. Satisfactory analysis of stage was precluded by the small stage II group. Five factors were significant predictors: measured depth of primary invasion, p equals 7x10(-7); anatomic depth, p equals 7x10(-6); NANA, p equals 0.003; age, p equals 0.005; and growth pattern (superficial spreading vs nodular) p equals 0.01. Only 2 of these predictors were independent; Measured depth and NANA. NANA may prove useful in identifying high risk MM pts, especially those with measured depth greater than 1.5 mm. (2 Refs)

32. URINARY EXCRETION OF MODIFIED NUCLEOSIDES IN CHRONIC MYELOGENOUS LEUKEMIA (MEETING ABSTRACT)

Heldman DA, Grever MR, Trewyn RW
Ohio State University, College of Medicine, Columbus, OH, 43210
Proc Am Soc Clin Oncol; 1:C-24 1982

Urinary excretion of modified nucleosides was measured in 15 patients with Philadelphia-chromosome-positive chronic myelogenous leukemia (CML) to determine their correlation with activity of this disease. Resolution and quantitation of 7 nucleosides was accomplished using reversed-phase high-performance liquid chromatography. Patients in the stable phase of CML had excretion levels 1-2 times normal, whereas patients in the blastic phase showed more marked elevations (up to 12 times normal). The nucleosides showing the most significant differences in median excretion between stable phase (CML-S) and blastic phase (CML-B) were pseudouridine, P; 1-methylinosine, m1I; and N2, N2-dimethylguanosine, m22G. Nucleoside excretion was also determined in patients with bacterial pneumonia and urinary tract infection for comparison. Serial nucleoside determinations made in a patient whose CML was initially stable showed an early and rapid rise of nucleoside excretion (especially m1I) with blastic transformation. We conclude that the degree of elevation and the correlation with disease activity demonstrate the potential value of urinary nucleoside quantitation in monitoring patients with CML; in particular, nucleoside excretion may be useful in detecting early blastic transformation. (no Refs)

33. MEASUREMENT OF URINARY PTERIDINES FOR THE DETECTION OF CANCER: EVALUATION OF THE RAO, ET AL METHOD.

Duvall S, Ridgway H, Speer RJ
Dept. Chemistry, Wadley Inst. Molecular Medicine, Dallas, TX, 75235
J Clin Hematol Oncol; 12(2):49-54 1982

The measurement of the urinary excretion of 6-hydroxymethyl pterin has been reported as a diagnostic test for the detection of cancer by RAO, et al. We were unable to confirm their findings. (Author abstract) (8 Refs)

34. NONSUPPRESSIBLE INSULIN-LIKE PROTEIN (NSILP) AS A TUMOUR MARKER FOR PATIENTS WITH SOFT TISSUE SARCOMAS (MEETING ABSTRACT)

Tannavikral P, Siu A, Poffenberger P, Cummings B, Harwood A, Quirt I
The Princess Margaret Hospital, Toronto, Ontario M4X 1K9, Canada
Proc Am Soc Clin Oncol; 1:C-664 1982

NSILP is a 90,000 molecular weight serum glycoprotein that exhibits insulin-like bioactivity. Marked elevation of the NSILP has been demonstrated in patients with retroperitoneal sarcoma associated with hypoglycemia. NSILP was assayed in 89 patients with soft tissue sarcoma and 14 control patients with other malignancies. No patients with elevated NSILP experienced symptomatic hypoglycemia. Five of the 7 patients with elevated NSILP but no clinical evidence of residual sarcoma at the time the NSILP was assayed have since recurred. NSILP is elevated in a significant proportion of patients with soft tissue sarcomas in the absence of symptomatic hypoglycemia. In some patients it may be the only indicator of residual disease. (no Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

35. INCREASED ACTIVITY OF A BETA-GALACTOSYLTRANSFERASE IN TISSUES OF RATS BEARING PROSTATE AND MAMMARY ADENOCARCINOMAS.

Jenis DM, Basu S, Pollard M
(c/o Basu) Lobund Lab., Dept. Chemistry, Univ. Notre Dame, Notre Dame, IN, 46556
Cancer Biochem Biophys; 6(1):37-45 1982

The levels of UDP-galactose:N-acetylglucosamine(beta1 4)galactosyltransferase activity (GalT-4) were determined in the sera, in solid tumors, and in corresponding cell cultures of rats bearing two lines of prostate adenocarcinomas (PA-2 and PA-3) and in the sera of rats bearing other transplanted and autochthonous adenocarcinomas. Sera and tissues from normal (tumor-free) rats were used as controls. Prostate adenocarcinoma cell cultures had 5x greater levels of enzyme activity than did tumor cell infiltrated lymph nodes from animals bearing the prostate adenocarcinomas. The levels of activity in the cells of both prostate tumor lines were equivalent, even though they metastasize through different routes. Serum levels of galactosyltransferase activity were elevated only in animals with prostate tumor line PA-2, in which tumor cells were detected in the blood, and in rats bearing a mammary adenocarcinoma with extensive necrosis of the tumor mass (tumor mass greater than 22.0 g/200 g body wt). The increase was 3x the

control value. The sera of L-W rats bearing prostate tumors (PA-2 and PA-3) were inactive with the GalNAc-containing acceptor, GM2 (GalNAcbeta1-4(NeuAcalpha2-3)Galbeta1-4Glc-Cer), but active with either free GlcNAc (Km = 0.25 mM) or LcOse3Cer (GlcNAcbeta1-3Galbeta1-4Glc-Cer; GlcNAc-R). (Author abstract) (38 Refs)

36. CHANGES IN ACTIVITIES OF URIDINE DIPHOSPHATE-GLUCURONYL-TRANSFERASES DURING CHEMICAL HEPATOCARCINOGENESIS.

Yin Z, Sato K, Tsuda H, Ito N
(c/o Sato) Second Dept. Biochemistry, Hirosaki Univ. Sch. Medicine, 5, Zaifu-cho, Hirosaki 036, Japan
Gan; 73(2):239-248 1982

Changes in the activities of hepatic uridine diphosphate-glucuronyltransferases (UDP-GTs) were investigated during the induction of hyperplastic nodules (enzyme-altered foci) by a system consisting of diethylnitrosamine (DEN) followed by N-2-fluorenylacetamide (FAA) and including partial hepatectomy. The activity of the late fetal form of UDP-GT, which was assayed towards o-aminophenol (o-GT activity), was induced rapidly by a single ip injection of DEN (200 mg/kg) or 3-methylcholanthrene (40 mg/kg) or by the continuous administration of FAA (0.02% in diet) alone. The activity further increased with the appearance of the nodules, while the activity of the neonatal form, which was assayed toward phenolphthalein (p-GT activity) and was inducible by phenobarbital, increased only slightly. The increased o-GT activity showed a good correlation with the increased number or area of enzyme-altered foci detected by gamma-glutamyltransferase activity staining, but the p-GT activity did not, though it was significantly increased. In hyperplastic nodules and well differentiated hepatomas induced by DEN (0.1% in drinking water, 3 wk) but isolated long after cessation of DEN, o-GT activity was markedly increased, but p-GT activity was decreased or remained at the level of normal rat liver. These data indicate that the increased o-GT activity may be one of the enzyme markers for preneoplastic hepatic cells. An antioxidant, butylated hydroxyanisole (BHA) (0.75% in diet), markedly elevated the hepatic o-GT activity rapidly after being administered with FAA in the above system, and the induction of the nodules was inhibited. (Author abstract) (32 Refs)

37. COVALENT CROSS-LINKING OF A PHOTOACTIVE DERIVATIVE OF CALCITONIN TO HUMAN BREAST CANCER CELL RECEPTORS.

Moseley JM, Findlay DM, Martin TJ, Gorman JJ
Dept. Medicine, Univ. Melbourne, Repatriation General Hosp., Heidelberg, Victoria, 3077, Australia
J Biol Chem; 257(10):5846-5851 1982

A photoaffinity derivative of salmon calcitonin has been produced by transglutaminase-mediated incorporation of N-(beta-aminoethyl)-4-azido-2-nitroaniline into the hormone. The derivative, purified by high pressure liquid chromatography, retained the abilities to bind to cultured T47D breast cancer cells and to stimulate adenylate cyclase in these cells. In both these respects it was equipotent with synthetic salmon calcitonin. Photolysis of the 125I-labeled photoactive salmon calcitonin derivative bound to T47D cells was accompanied by specific labeling to only one component (Mr = 85,000) as assessed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Labeling was observed only upon photolysis and was inhibited by unlabeled synthetic salmon calcitonin but not by the inactive calcitonin analogue, 8-glycine human calcitonin. Reduction did not alter the apparent mol wt of the calcitonin receptor complex. No macromolecular forms of calcitonin were produced by photolysis in the absence of T47D cells. (Author abstract) (29 Refs)

38. A NEW MARKER FOR HORMONAL RESPONSIVENESS OF RAT MAMMARY TUMORS (MEETING ABSTRACT).

Liu DK
Department of Pharmacology, Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, PA, 17033
Proc Am Assoc Cancer Res; 23:910 1982

We previously reported a mammary-specific, Ca++-stimulated ribonuclease (Ca++-RNase) whose activity in normal mammary gland parallels the degree of differentiation. To determine whether this enzyme can serve as a marker for hormonal responsiveness, we have assayed the activity in a series of rat mammary tumors of varying orgin. RNase activity of an ammonium sulfate extract prepared from whole tissue homogenate was assayed under various ionic conditions, using (3H)poly(U) as substrate. Although the rate of poly(U) degradation varied according to the ionic conditions of the assay for a given tumor extract and also between tumor extracts under the same assay conditions, a general pattern emerged. In MT/9, MT/9a, DMBA 1, DMBA 8, DMBA 14 and R3230AC tumors, the activity assayed in the presence of CA++, or Ca++ plus EDTA, reflecting Ca++-RNase activity was 4 to 5 times higher than the activity assayed with Mg++ and 100 to 700 times that in the presence of EDTA alone. These tumors are all known to be estrogen-responsive mammary adenocarcinomas. High Ca++-RNase activity was also present in the estrogen-sensitive 3M2N squamous cell carcinoma. Conversely, RNase activity assayed with Ca++ present was lower than that with either Mg++ or no added ion in MAMF2-TC, SMT-2A and 13762 mammary tumors, all undifferentiated, poorly differentiated or estrogen unresponsive mammary carcinomas. The same is true for mammary fibroadenomas. These results show that Ca++-RNase, which is easily detected in crude tumor extracts, is a useful marker in characterization of rat mammary tumors with respect to estrogen responsiveness. (no Refs)

39. HETEROGENEITY OF MLR-S EXPRESSION IN HUMAN LEUKEMIC T-CELL LINES: EVIDENCE FOR MLR-S EXPRESSION AT THE LATE T-BLAST STAGES OF T-CELL DIFFERENTIATION (MEETING ABSTRACT)

Han T, Minowada J, Dadey B, Ozer H
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:977 1982

The absence of Ia-like antigen and of stimulating capacity in 'one-way' mixed lymphocyte reaction (MLR-S) is thought to be a common feature of all T-cell leukemia-lymphoma lines. Recently, several T-cell leukemia-lymphoma lines with Ia-like antigen have been established and characterized. In the present study the MLR-S expression status of 16 T-cell leukemia-lymphoma lines and correlations between the MLR-S expression and Ia-like antigen as well as other phenotypic markers are determined. The results of MLR-S of these 16 T-cell lines are as follows: Seven T-cell lines exerted a strong MLR-S when a 1:1 ratio of responders to stimulators was utilized. Of the 9 T-cell lines with no MLR-S at a 1:1 ratio of responders to stimulators, 6 T-cell lines elicited a low but significant MLR-S when a 1:2 or 1:4 ratio of responders to stimulators was utilized. The remaining 3 T-cell lines remained nonstimulatory even though higher numbers of stimulating cells were utilized. Each of 6 T-

cell lines with Ia-like antigen was found to be capable of exerting a significant MLR-S. All 3 T-cell lines without Ia-like antigen, on the other hand, exerted no MLR-S. In all cALL antigen-negative and TdT(terminal deoxynucleotidyl transferase)-negative T-cell lines (late T-blast stages), the MLR-S was either strong or moderate but never absent, whereas in all T-cell lines with both TdT and cALL or with TdT and without cALL antigen (early T-blast stages), the MLR-S was either absent or very weak. These observations support the speculation that the presence of MLR-S, like Ia-like antigen expression, may be associated not with the early but rather the later T-blast stages of T-cell differentiation. (no Refs)

40. IMMUNOMODULATION BY IFN-CONJUGATED MONOCLONAL ANTIBODY TO HUMAN OSTEOGENIC SARCOMA (MEETING ABSTRACT)

Baldwin RW, Flannery GR, Pelham JM, Gray JD
Cancer Research Campaign Laboratories, University of Nottingham, University Park, Nottingham NG7 2RD, England
Proc Am Assoc Cancer Res; 23:1003 1982

Purified human lymphoblastoid interferon-alpha (IFN-alpha) has been coupled covalently, using N-succinimidyl 3-(2-pyridyldithio) proprionate (SPDP), to a mouse monoclonal antibody raised against the human osteogenic sarcoma cell line 791T. This antibody has been described elsewhere and binds specifically to cells of the immunizing tumor and to a number of other osteogenic sarcoma cell lines. The purified conjugate retains both antibody activity and IFN activity: binding to 791T cells can be shown in competitive binding assays using fluorescent-labelled antibody and the Fluorescence Activated Cell Sorter (FACS IV), and human peripheral blood lymphocyte-mediated lysis of 791T cells and the erythroleukemic cell line K562, is significantly enhanced after 1 hr incubation with effector cells. The antibody has been shown to localize in 791T xenografts in immunodeficient mice. The conjugate has been tested in an in vitro model system: in the presence of IFN-antibody conjugate bound to 791T cells, human NK cells exhibit significantly enhanced killing of a second, radiolabelled target (K562). Pre-incubation of mixtures of IFN and antibody with 791T cells failed to produce NK cell stimulation. This reagent represents a novel and potentially effective therapeutic tool which may allow specific targetting of IFN to the tumor site in vivo and subsequent activation of tumor-infiltrating NK cells. (1 Ref)

41. SPECIFICITY AND TUMOR LOCALIZATION OF A MONCLONAL ANTIBODY (MA) DEFINING A HUMAN GLIOMA ASSOCIATED EXTRACELLULAR MATRIX ANTIGEN (MEETING ABSTRACT)

Bourdon MA, Wikstrand CJ, Coleman RE, Bigner DD
Duke University Medical Center, Durham, NC
Abstracts of the 58th Annual Meeting, June 11-13, 1982, Philadelphia, Pennsylvania. American Association of Neuropathologists 386 pp., 1981.

We have used MA81C6, generated against the glial fibrillary acidic protein positive human glioma cell line U-251MG, to examine the distribution and localization of a glioma-mesenchymal extracellular membrane, but not normal brain. Cell line and tissue specificities were assayed by cell surface radioimmunoassay (RIA), absorption analysis, and peroxidase-antiperoxidase (PAP) immunohistology. 131-I-MA81C6 tumor localization in U-251M6 nude mouse xenografts was examined by radioscintigraphy. MA81C6 specificity analysis showed that GMEM was present in extracellular matrix (ECM) of glioma cell lines (14/16), glioma xenografts (7/9), and proliferative endothelial basement membranes of GBM (10/11). GMEM was also expressed by cells of mesenchymal origin including sarcoma (2/6) and fibroblast (8/9) cell lines and ECM of liver and spleen sinusoids and kidney medulla. GMEM was not detected in adult and fetal brain, muscle, skin, meningiomas, medulloblastoma, and astrocytomas (5/6) examined. By RIA and PAP, MA81C6 did not cross-react with fibronectin, laminin, or collagen types I-V. 131-I-MA81C6 tumor localization in U-251MG-bearing nude mice showed specific MA81C6 localization in the glioma xenografts; in paired labeled experiments using a 125-I-labeled control immunoglobulin, tumors were clearly imaged by 131-I-radioscintigraphy within 48 hrs. (no Refs)

42. GROWTH FACTORS IN HODGKIN'S DISEASE.

Ford RJ, Mehta S, Davis F, Maizel AL
Dept. Anatomic Pathology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77025
Cancer Treat Rep; 66(4):633-638 1982

Tumor nodules from spleens removed at staging laparotomy for nodular sclerosing Hodgkin's disease were grown as fragment cultures in vitro. These cultures could be maintained in vitro for up to 2 months and consisted of 90% large, adherent multinuclear and mononuclear cells. Immunologic markers and enzyme histochemistry suggested that the cultured cells belonged to the monocyte/macrophage lineage. Supernatants from these cell cultures were then assayed for the monokine Interleukin 1 and for fibroblast stimulatory factors, which were both present. These results are discussed in considering Hodgkin's disease as a neoplasm of the monocyte/macrophage lineage, capable of producing functionally active mediators that may account for the histopathologic appearance observed. (Author abstract) (20 Refs)

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. PROGNOSTIC VALUE OF PREOPERATIVE SERUM CEA LEVEL COMPARED TO CLINICAL STAGING: II. STOMACH CANCER.

Staab HJ, Anderer FA, Brummendorf T, Hornung A, Fischer R
Friedrich Miescher Laboratorium, Max Planck Gesellschaft, Spemannstr. 37-39, 7400 Tübingen, W. Germany
Br J Cancer; 45(5):718-727 1982

In a clinical investigation of postoperative survival after primary surgery for stomach cancer, 390 patients were registered since 1974. The potential prognostic parameters examined within the first days of hospitalization for primary resection included age of the patients, operability, tumor extension (TNM classification) and tumor Stages I-IV (UICC). Statistical treatment of the data revealed that each of the clinical parameters covers critical ranges associated with highly significant differences in patient survival. The preoperative serum CEA concentration exhibited prognostic significance in addition to the criteria of operability and tumor extension. In selected sub-

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groups of patients with distinct resectability and tumor extension, ranges of preoperative CEA concentration could be specified which were associated with statistically significant differences in the patient survival. The results indicate that the preoperative serum CEA level can be an independent prognostic parameter in stomach cancer. (Author abstract) (15 Refs)

2. CARCINOEMBRYONIC ANTIGEN AS A MONITOR OF RECURRENT BREAST CANCER.

Lee YT

Dept. Surgery, LAC-Univ. Southern California Medical Center, Los Angeles, CA, 90033

J Surg Oncol; 20(2):109-114 1982

Carcinoembryonic antigen (CEA) test was performed at the time of diagnosis in 136 patients with early operable breast carcinoma (Stage I = 65, Stage II = 71). Only 4% had CEA levels greater than 5 ng/ml. Patients with axillary metastasis (Stage II) had higher incidence of abnormal CEAs than those with disease localized to the breast (Stage I). Follow-up CEA tests were performed on 243 patients after mastectomy. In this group, 50 patients developed recurrent disease and 48% had elevated CEA levels. Patients with chest-wall recurrences rarely had abnormal CEAs, while those with visceral metastasis had higher levels. Among the 193 patients known to be without recurrence, 10% also had elevated CEAs. Excluding inflammatory, hepatic, and renal diseases, the most common medical conditions which could explain such false elevations are diabetes, hypertension, and organic heart disease. (Author abstract) (22 Refs)

3. URINARY CEA FOR PREDICTION OF SURVIVAL TIME AND RECURRENCE IN BLADDER CANCER.

Wahren B, Nilsson B, Zimmerman R

Dept. Virology, Natl. Bacteriological Lab., S-105 21 Stockholm, Sweden

Cancer; 50(1):139-145 1982

The prognostic information from carcinoembryonic antigen was evaluated in bacteria-free urines of patients with bladder carcinoma. Patients with elevated (greater than or equal to 30 ng/ml) U-CEA had a poorer relative and symptom-free survival than patients with initial U-CEA below 30 ng/ml. Patients in whom U-CEA decreased from before to after radiation treatment had a better survival rate than patients with increasing U-CEA. These findings were most significant in cases with large (T3 + T4) tumors or with tumors of a lower differentiation (G3). U-CEA appeared to be an independent variable for prognostic evaluation of survival, since these differences were also true within the subgroups of known variables such as classes or grades. All but one of the patients, in whom short-term local control was obtained, had a posttreatment U-CEA below 50 ng/ml. In oncology units, where the more malignant bladder tumors are treated, U-CEA determinations may indicate which patients require intensified monitoring or treatment. (Author abstract) (27 Refs)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

4. CLINICAL VALUE OF DIFFERENT METHODS FOR DETERMINATION OF ACID PHOSPHATASE IN PROSTATIC CANCER.

Fluchter SH, Bichler KH, Harzmann R, Reuter MA, Mildner A

Dept. Urology, Univ. Tubingen, Calwerstrasse 7, D-7400 Tubingen, W. Germany

Urol Int; 37(2):79-86 1982

The availability of a radioimmunoassay (RIA) and an enzyme immunoassay (EIA) for the prostate specific acid phosphatase required a study to compare these techniques with the conventional colorimetric assay. Our study is based on examinations of 188 normal persons and 136 patients with carcinoma of the prostate. The advantage of the immunologic methods - RIA and EIA - lies in their stable immunologic activity and their high specificity. However, RIA and EIA are not screening methods for incidental carcinoma because of their low sensitivity for Stage-A tumors. Their good sensitivity at lower ranges of concentration makes them suitable for checking the course of a prostatic carcinoma during therapy. The level of prostatic acid phosphatase may allow conclusions about intra- or extracapsular growth of the prostatic carcinoma. (Author abstract) (28 Refs)

5. CREATINE KINASE ISOENZYME (CK-BB) IN COMBINATION TO PROSTATIC ACID PHOSPHATASE MEASURED BY RIA IN THE DIAGNOSIS OF PROSTATIC CANCER.

Huber PR, Zaugg T, Linder E, Hagmaier V, Rutishauser G

Hormone Lab., Dept. Gynaecology, Kantonsspital Basel, CH-4031 Basel, Switzerland

Urol Res; 10(2):75-80 1982

The diagnostic value of combining estimation of creatine kinase iosenzyme (CK-BB) and prostatic acid phosphatase (PAP) in cases of suspected prostatic cancer was investigated. CK-BB was determined using radioimmunoassay specific for the isoenzyme. PAP was determined using the PAP test of Clinical Assays, which allows some differentiation between normal and benign hyperplasia of the prostate (BHP) and/or early stages of prostatic carcinoma. Only 1/14 sera from untreated patients had increased CK-BB, while 13 (30%) samples from treated patients had increases. Overall, only 10% of untreated and 25-30% of treated patients had concentrations of CK-BB greater than 7.5 ug/liter. When measured simultaneously with PAP, CK-BB levels did not add any information to that obtained by PAP estimation alone. Thus, CK-BB is not suitable as a tumor marker for detection of early stages of prostatic tumors. In single cases, however, CK-BB elevation above normal limits can indicate a tumor where PAP is still normal. CK-BB estimation alone by radioimmunoassay is not recommended as a marker for prostatic carcinoma, but the test can be applied in single cases to determination of follow up therapy or progress of disease. (22 Refs)

6. EVALUATION OF 5'-NUCLEOTIDE PHOSPHODIESTERASE ISOZYME-V AS A PREDICTOR FOR LIVER METASTASIS IN BREAST CANCER PATIENTS.

Tsou KC, Lo KW, Rosato EF, Yuk A, Enterline H, Schwegman C
1515 Ravdin Inst., Hosp. Univ. Pennsylvania, 3400 Spruce St., Phila, 19104
Cancer; 50(2):191-196 1982

The compound 5'-nucleotide phosphodiesterase isozyme-V (5'-NPD-V) was evaluated in 85 biopsy proven breast cancer patients as a potential marker for early liver metastasis. It correctly predicts liver metastasis in 85.7% patients with abnormal radiologic liver scan and 100% other patients with palpable liver. Serum glutamic-oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), alkaline phosphatase (AP) and total bilirubin (B) were also determined in 79 of these patients as routing liver function tests (LFT). Forty-one out of 79 from this group had all four markers all within normal limits. Yet of the 41 patients, 12 patients were found positive for 5'-NPD-V. Of these 12, one was found to have liver metastasis at surgery and one had abnormal liver scan. Five other patients had liver dysfunction and one had been diagnosed as an alcoholic. Four others had no evidence of either liver problems or liver metastasis, but follow-up data were lacking. This retrospective study, therefore, suggests that there is a definite advantage to include the 5'-NPD-V in the liver profile studies for breast cancer patients, although a positive 5'NPD-V may only indicate liver repair or liver regeneration. Long-term prospective studies of these tests with breast cancer patients should be worthwhile. No relation was found between 5'-NPD-V and axillary lymph node involvement or the estrogen receptor status of the excised tumor. Thus there is no evidence currently that the appearance of the 5'-NPD-V in serum is related to lymph node metastases or hormonal control. (Author abstract) (43 Refs)

7. PLACENTAL ALKALINE PHOSPHATASE AS A TUMOR MARKER FOR SEMINOMA.

Lange PH, Millan JL, Stigbrand T, Vessella RL, Ruoslahti E, Fishman WH
Dept. Urologic Surgery, Univ. Minnesota Health Sciences, Box 394, Mayo Memorial Building, Minneapolis, MN, 55455
Cancer Res; 42(8):3244-3247 1982

A sensitive and specific enzyme-linked immunoabsorbent assay was used in a retrospective study of serum levels of placental alkaline phosphatase (PLAP) in testicular cancer. Sixteen of 28 men with active seminoma had elevated PLAP levels, and 71% had elevated levels of either PLAP, human chorionic gonadotropin, or both. Only 4 of 22 men with active nonseminomatous cancer had elevated PLAP levels, and the levels were normal in all control patients, including 33 men apparently cured of testicular cancer. In 6 of 10 serial studies, PLAP levels provided information not otherwise available that would have been useful clinically, and the levels never were elevated inappropriately. Our data suggest that PLAP is a clinically useful serum tumor marker for seminoma. (Author abstract) (23 Refs)

8. THYMIDINE KINASE ACTIVITY IN ORAL SQUAMOUS CELL CARCINOMA.

Scully C
Univ. Dept. Oral Medicine and Oral Pathology, Glasgow Dental Hosp. and Sch., 378 Sauchiehall St., Glasgow, Scotland
J Oral Pathol; 11(3):210-213 1982

Serum thymidine kinase (TdR kinase) activity was determined in 30 patients with histologically confirmed oral squamous carcinoma and in 30 controls. The enzyme activity was significantly higher in patients with oral squamous cell carcinoma, particularly in those with regional lymph node involvement. TdR kinase activity may fall postoperatively in patients without recurrent disease. (20 Refs)

9. SIALYLTRANSFERASE ACTIVITY IN LEUKEMIA.

Sasaki R, Takaku F, Lin YL, Bollum FJ
Dept. Hematology, Jichi Medical Sch., 311-1 Yakushiji Minamikawachi-Machi, Kawaschi-Gun, Tochigi 329-04, Japan
Leuk Res; 6(2):197-202 1982

Assayed sialyltransferase activity (STA) in blasts from various types of leukemia patients was compared with the level of activity in mature lymphocytes or granulocytes. STA in blasts from acute lymphoblastic leukemia (ALL) patients was markedly lower (1.68 +-1.23 picomole; pmol/mg protein) than those (6.18 +-2.22 pmol/mg protein) of lymphocytes from the peripheral blood of normal volunteers. Also, in blasts from terminal transferase (TdT)-positive chronic myeloid leukemia (CML) patients in blasts crisis, a low level of the enzyme activity compatible to those of ALL patients was observed. STA was significantly increased in blasts (1.21 +-0.38 pmol/mg protein) from patients with acute non-lymphoblastic leukemia including acute myeloblastic leukemia, acute myelomonocytic leukemia, and acute promyelocytic leukemia, compared to the level of mature granulocytes (0.53 +-0.32 pmol/mg protein). However, only a slight difference was observed between the level of STA in the granulocytes from CML patients in chronic phases and in the granulocytes from normal volunteers. In TdT-negative CML in blast crisis, STA (2.11 +-0.88 pmol/mg protein) was significantly higher than those of mature granulocytes from normal controls, whereas no significant difference of the enzyme activity was noted between the blasts from TdT-positive CML in blast crisis and from ALL. (27 Refs)

10. UNUSUAL BIOCHEMICAL PATTERN OF SERUM ADENOSINE DEAMINASE ACTIVITY IN ACUTE LYMPHOBLASTIC LEUKAEMIA.

Gakis C, Piras MA, Romani G
Clinica delle Malattie infettive dell'Universita di Sassari, via Manno, 54-07100 Sassari, Italy
Haematologica (Pavia); 67(2):199-206 1982

Twenty-nine patients with leukemia (11 acute lymphoblastic leukemia, ALL; 6 chronic lymphocytic leukemia; 1 acute myeloid leukemia; 8 chronic myeloid leukemia; 2 subacute monocytic leukemia; and 1 blastic leukemia of uncertain classification, BL) were tested for adenosine deaminase activity (ADA) in serum. Most patients were diagnosed for the first time and were receiving no therapy. Normal sera were obtained from 17 healthy volunteers. The ADA for relative substrate specificity revealed two different enzymatic patterns within the ALL group. Treated patients had a deaminase ratio of 0.30 and 0.37 respectively, consistent with the 'serum type' enzyme present in other disease conditions previously studied. Untreated patients displayed a major activity on 2'deoxyadenosine with a deaminase ratio ranging from 0.51-0.72 consistent with the 'tissue type' enzyme. Individual values of deaminase ratio are shown indicating how the ratio enables differential diagnosis, whereas the assay on ADA alone does not. A curve with an optimum pH from 6.0-7.0 characterized the serum enzyme in viral hepatitis and 'null' cell ALL in remission, whereas both 'undifferentiated' and 'T-cell' ALL in acute phase displayed a curve with optimal pH between 7.0-7.7 overlapping that of lymphocyte lysate. Moreover, the substrate-activity curves

confirmed in two cases a tissue type Km much lower than in 'null' cell ALL in remission. In other groups, the only patient showing similar biochemical properties in the serum enzyme activity had BL. (13 Refs)

11. THE CORRELATION OF ADENOSINE DEAMINASE AND PURINE NUCLEOSIDE PHOSPHORYLASE ACTIVITIES IN HUMAN LYMPHOCYTES SUBPOPULATIONS AND IN VARIOUS LYMPHOID MALIGNANCIES.

Demeocq F, Viallard JL, Boumsell L, Richard Y, Chassagne J, Plagne R, Lemerle J, Bernard A
Centre Jean Perrin, B. P. 392, 63011 Clermont-Ferrand Cedex, France
Leuk Res; 6(2):211-220 1982

Activities of adenosine deaminase (ADA) and purine nucleotide phosphorylase (PNP) were measured in normal human T cells and in the tumor cell populations from 62 children and 27 adults with lymphoid malignancies. Thymocytes had high ADA activity and low PNP activity, whereas T-peripheral blood lymphocytes (PBL) had low ADA activity and high PNP activity. Malignant B-cell populations had low values of ADA activities and intermediate values of PNP activities similar to E rosette formation negative PBL. Non-T, non-B acute lymphocytic leukemia (ALL) patients had cells with high values of ADA activities and moderate values of PNP activities. A linear correlation between ADA and PNP activities was observed in cells from non-T, non-B ALL, whereas such a correlation did not appear in cells from T-ALL or T-lymphoblastic lymphomas. HLA-DR negative common ALL cell populations had high values of ADA as compared to HLA-DR positive common ALL cell populations. In contrast with HLA-DR, presence or absence of common ALL antigen, as defined by Mo.Ab J5, did not appear to correlate with the level of the enzyme activities. Particularly no clear distinction between the subgroup of malignancies that could be related to corticothymocytes and the subgroup related to medullary thymocyte in terms of both ADA and PNP activities could be disclosed, and large ranges of values were observed in both subgroups. No correlation appeared to occur in the group of T-cell lymphoid malignancies, whereas a correlation existed in cells from children with non-T, non-B ALL. (37 Refs)

12. HIGH LEVELS OF IMMUNOREACTIVE NERVOUS SYSTEM-SPECIFIC ENOLASE SERA OF PATIENTS WITH NEUROBLASTOMA.

Ishiguro Y, Kato K, Shimizu A, Ito T, Nagaya M
Dept. Biochemistry, Inst. for Developmental Res., Aichi Prefectural Colony, Kasuya, Kasugai, Aichi 480-03, Japan
Clin Chim Acta; 121(2):173-180 1982

A sensitive determination of serum nervous system-specific enolase (NSE) using an enzyme immunoassay system is described and increased NSE levels in patients with neuroblastoma are reported. The assay of human NSE was carried out with a sandwich enzyme immunoassay system for rat NSE using cross reactivity of human gamma subunit to the antibody to rat gamma subunit. Infant control samples were sera from 20 patients (15 males, 5 females, 1-7 yr old) without disease. Adult control samples were obtained from 20 healthy individuals (10 males, 10 females, 20-40 yr old). Serum samples with neuroblastoma were obtained from patients undergoing treatment. Clinical data on the patients examined are presented. Standard curves of rat (RGG) and human gamma gamma (HGG) enolases and the cross-reactivities of other forms of human enolase are presented. The reactivity of HGG enolase of the assay was approx 30% that of RGG, when assessed by comparing the amounts of HGG and RGG required to display a fluorescence intensity of 50% bound beta-D-galactosidase activity. When serum samples from normal individuals and patients with neuroblastoma were subjected to the assay after various dilutions with buffer G, almost parallel curve slopes were observed. These results indicated that the serum levels of NSE could be determined with the applied immunoassay. NSE levels in serum with neuroblastoma ranged from 13.6-330 nanog (ng)/ml (mean 96 ng/ml) which was approx 30-and 20-fold higher than that in the adult and infant control levels, respectively. NSE levels in serum with ganglioneuroblastoma were near the normal ranges. Results suggested that NSE in serum might be a useful marker for screening and therapeutic monitoring of neuroblastoma. (17 Refs)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

13. ESTROGEN RECEPTORS IN PRIMARY BREAST CANCER.

Neifeld JP, Lawrence W, Brown PW, Banks WL, Terz JJ
Medical Coll. Virginia, Virginia Commonwealth Univ., Box 11, MCV Station, Richmond, VA, 23298
Arch Surg; 117(6):753-757 1982

Estrogen receptor (ER) activity was assayed in 132 patients undergoing mastectomy for primary breast cancer and in 75 patients whose initial treatment for metastatic cancer was endocrine manipulation. Estrogen receptor status correlated with response to endocrine therapy. Among patients whose ER activity was assayed in the primary tumor, ER-positive patients had an improved disease-free survival (independent of stage or nodal or menopausal status) after mastectomy when compared with ER-negative patients (p less than 0.05). The ER-positive and ER-negative patients receiving adjuvant chemotherapy had similar disease-free survivals. These data confirm that patients with ER-positive primary tumors have a better prognosis than patients with ER-negative primary tumors. Although adjuvant chemotherapy improves the prognosis in patients with histologically positive lymph nodes in both ER-positive and ER-negative patients, the disease-free survivals in ER-negative patients may improve to a greater extent than in ER-positive patients. (Author abstract) (15 Refs)

14. ESTROGEN RECEPTOR PROTEIN IN ADENOMAS OF THE LARGE BOWEL.

Agrez MV, Spencer RJ
(c/o Spencer) Dept. Colorectal Surgery, Mayo Clinic, 200 First St. Southwest, Rochester, MN, 55905
Dis Colon Rectum; 25(4):348-350 1982

Thirty adenomas of the large bowel, removed from 15 females and 15 males, were examined for the presence of estrogen receptor protein. The finding of positive binding capacity in 2 of the 30 adenomas supports the hypothesis that hormonal dependency does not play a major role in the development and growth of colorectal adenomas. (Author abstract) (15 Refs)

15. A MICRO-ASSAY FOR ESTROGEN RECEPTOR IN BREAST TUMOR WITH USE OF 125I-LABELED ESTRADIOL.

Van NT, Fritsche HA, Trujillo JM
Dept. Lab. Medicine, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. at Houston, Houston, TX, 77030
Clin Chem; 28(6):1303-1308 1982

The concentration of estrogen receptor protein in breast-tumor tissue is generally expressed in units of femtomoles of estradiol bound by the receptor per milligram of cytosol protein. The sensitivity of the estrogen receptor radioligand assay is therefore related to the specific activity of the steroid label used for the binding assay, the amount of the receptor protein in the vol of cytosol used, and the protein concentration in the cytosol. In this paper, we discuss factors affecting the sensitivity of the estrogen receptor assay and present various approaches for optimizing the assay. We also describe a procedure that involves a radioiodinated estradiol of high specific activity, a micro-technique for preparing tumor cytosol, and a micro-assay procedure with which the estrogen receptor protein can be measured in as little as 50 mg (wet weight) of tissue. (Author abstract) (7 Refs)

16. TWO AIDS IN OESTROGEN RECEPTOR CHARACTERISATION.

Smyth CM, Reeve TS
Dept. Surgery, Univ. Sydney, Royal North Shore Hosp., Wallace Freeborn Professional Block, St. Leonards 2065, New South Wales, Australia
Aust NZ J Surg; 52(2):161-164 1982

Eighty three breast carcinoma primary and metastatic lesions were submitted for estrogen receptor (ER) assessment using a standard dextran coated charcoal saturation analysis (0.1 nM - 08 nM tritiated estradiol), as well as a single saturating dose (SSD) assay (8 nM tritiated estradiol). Excellent correlation between the two methods was demonstrated. The single dose assay also provided additional information to aid the construction of adequate Scatchard plots in those biopsies which exhibited high levels of specific receptor proteins. Three hundred and fifteen consecutive breast carcinoma primary or metastatic lesions, assessed for ER, had imprint cytological examinations to verify the malignancy of the specimen. Seven percent demonstrated sparse epithelial cellularity with a low or nil malignant cell proportion and showed a lower receptor positivity than the remaining specimens. (Author abstract) (10 Refs)

17. BIOCHEMICAL ASSESSMENT OF HISTOCHEMICAL METHODS FOR OESTROGEN RECEPTOR LOCALISATION.

Underwood JC, Sher E, Reed M, Eisman JA, Martin TJ
Dept. Pathology, Univ. Sheffield Medical Sch., Beech Hill Road, Sheffield S10 2RX, England
J Clin Pathol; 35(4):401-406 1982

The biochemical validity of published labeled-ligand and ligand-antibody methods for the histological localization of estrogen receptors (ER) in breast carcinomas was assessed by measuring specific and non-specific binding of 3H-estradiol to pretreated MCF-7 monolayers; the monolayers had been either frozen and thawed, then air-dried or acetone-fixed, or fixed in formaldehyde to reproduce the conditions in published methods. The results indicate that most of the ER in a frozen section is likely to be lost by diffusion into the supernatant incubation medium. Fixation substantially restricts diffusion but reduces specific estradiol binding and may increase non-specific binding; acetone fixation is particularly deleterious. Preincubation in estradiol fails to protect the receptor during fixation. We conclude that the published histochemical methods for ER localization have doubtful validity and should not yet be used in preference to conventional biochemical assays. (Author abstract) (22 Refs)

18. IMMUNOREACTIVE SERUM CALCITONIN IN PATIENTS WITH MAMMARY CARCINOMA.

Fereberger W, Leb G, Passath A, Samonigg H, Beaufort F
Medizinische Klinik der Universitat, Auenbruggerplatz 11, A-8036 Graz, Austria
MMW; 124(19):471-472 1982

Serum calcitonin levels in 50 women with mammary carcinoma were measured by means of a 125I radioimmunoassay. Twenty healthy men served as controls. Bone metastases were diagnosed in 36/50 women. Elevated levels of calcitonin were found in 6/50 women; these 6 women had varying degrees of disease progression. Levels for the entire group of the patients did not differ significantly from those for the controls. Serum calcitonin is therefore not of value as a tumor marker in patients with mammary carcinoma. (9 Refs) (In GER)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

19. EXPRESSION OF DR ANTIGENS IN FRESHLY FROZEN HUMAN TUMORS.

Thompson JJ, Herlyn MF, Elder DE, Clark WH, Steplewski Z, Koprowski H
Div. Surgical Pathology, Hosp. Univ. Pennsylvania, Box 527, 3400 Spruce St., Philadelphia, PA, 19104
Hybridoma; 1(2):161-168 1982

Using frozen tissue sections, a monoclonal antibody (WI 691-13-17) known to detect an epitope common to all DR antigens on the beta (light) chain of DR antigens, and a two-step indirect immunoperoxidase technique, DR antigens were found on all metastatic lesions tested and on many primary tumors and their histogenetic precursors. In all, 106 benign and malignant tumors and 255 normal tissues were tested. All metastatic and most of the primary tumors apparently expressed DR antigens; malignancies derived from ectodermal, endodermal, and mesodermal embryonic layers all showed DR expression. DR antigen expression was seen in all lesions of the melanocytic neoplastic system as defined by Elder and co-workers, with precursor lesions demonstrating relatively few positive cells, primary and metastatic lesions progressively more. A subpopulation of lymphocytes, macrophages, endothelial cells, and Langerhans cells also exhibited DR antigen expression. The quantitative intensity of staining among the cells of the lesions tested ranged from negative to variable amounts. This technique allows individual cells to be assessed for antigen expression and presumably more accurately reflects in vivo antigen expression than results obtained from cells selected by tissue culture methods. (13 Refs)

20. EVIDENCE THAT HEPATITIS B VIRUS HAS A ROLE IN LIVER-CELL CARCINOMA IN ALCOHOLIC LIVER DISEASE.

Brechot C, Nalpas B, Courouce AM, Duhamel G, Callard P, Carnot F, Tiollais P, Berthelot P
Unite de Recombinaison et Expression Genetique, Institut Pasteur, 28 rue du Docteur Roux, 75015 Paris, France
N Engl J Med; 306(23):1384-1387 1982

Determinations of hepatitis B virus (HBV) DNA were made in a prospective study of 51 alcoholics without hepatocellular carcinoma (HCC) and in a retrospective study of 20 alcoholics with both alcoholic cirrhosis and HCC. The overall prevalence of HBV serologic markers was 37% in the first group, compared with 10% in a nonselected blood-donor population. HBV DNA was detected in liver samples from three hepatitis B surface antigen (HBsAg)-positive patients from the first group and in liver samples of five other patients from this group in whom serum HBsAg was not detectable. In the second group, HBV DNA was detected in the neoplastic portion of the autopsied liver in all patients. Integration of viral DNA into the hepatocellular DNA was demonstrated in the samples from the second group, but conclusively in only two samples from the first group. HBV DNA was not detected in the livers of 14/16 patients with alcoholic liver disease (from the first group) who were negative for HBsAg but positive for anti-hepatitis B core antigen or anti-HBsAG, suggesting that HBV is probably not involved in progression of the liver disease. The presence of HBV DNA in livers of alcoholic patients without HCC may delineate the population at high risk for development of this disease. (25 Refs)

21. BLOOD GROUP PRECURSOR T-ANTIGEN EXPRESSION IN HUMAN URINARY BLADDER CARCINOMA.

Coon JS, Weinstein RS, Summers JL
Dept. Pathology, Rush-Presbyterian-St. Luke's Medical Center, 1753 W. Congress Parkway, Chicago, IL, 60612
Am J Clin Pathol; 77(6):692-699 1982

Tumor deletion of the ABH blood group antigens (BGAg) heralds an unfavorable prognosis in human bladder cancer. The T antigen (Thomsen-Friedenreich antigen: TAg), a precursor of other BGAg, has previously been found in malignant but not most normal cells, in which the TAg is cryptic but can be unmasked with neuraminidase (NMD). We investigated the prognostic significance of TAg expression in bladder cancer by staining paraffin sections with a T-specific lectin (peanut agglutinin [PNA]) immunoperoxidase technic. Seventy-two cases of low grade, low stage bladder cancer, 21 cases of high grade bladder cancer, and 68 controls were studied. All normals expressed the TAg only after NMD treatment (Cryptic TAg+). The Grade III cancers, all invasive, either expressed the TAg (TAg+) (67%) or lacked T even after NMD (Cryptic TAg-) (29%), indicating that the T structure was lost rather than masked as in normal tissue. Thirty-nine percent of 23 Grade I and II cancers which were TAg+ or Cryptic TAg- subsequently became invasive (Stage B), compared with 10% of 49 Cryptic TAg+ cancers. For 32 Grade I and II, ABH BGAg negative cancers, 64% of TAg+ or Cryptic TAg- cancers became invasive, compared with 17% of cancers which had Cryptic TAg+. Thus, the TAg may be a prognostically useful immunohistochemical tumor marker in bladder cancer, especially for tumors negative for ABH BGAg. (Author abstract) (37 Refs)

22. SURFACE ANTIGENIC PHENOTYPES OF HUMAN T-CELL LEUKEMIA CORRESPONDING TO THOSE OF POST-THYMIC T CELLS.

Ishii Y, Fujimoto J, Kon S, Ogasawara M, Koshiba H, Mikuni C, Kikuchi K
Dept. Pathology, Sapporo Medical Coll., S1 W17, Sapporo 060, Japan
Am J Hematol; 12(3):251-260 1982

Leukemic cells from eight adult patients with various types of T-cell leukemias, including one patient with lymphosarcoma cell leukemia (T-LSL), two patients with chronic lymphocytic leukemia (T-CLL), and five patients with adult T-cell leukemia (ATL), were analyzed for their surface antigenic phenotypes with a series of monoclonal antibodies directing to human T-cell differentiation antigens. All of the leukemic T cells studied were regarded as being of post-thymic T-cell origin because of their ability to form rosettes with sheep red cells under the condition at 4 C but not 37 C as well as the expression of human Ly-1-like but not TL-like antigen on their cell surfaces. By using monoclonal antibodies to a variety of human T-cell antigens (Leu-1, Leu-2a, and Leu-3a), all eight cases could be divided into either group of three distinct categories. Thus, one patient with T-LSL had cells with Leu-1+2a+3a+ phenotype, which might reflect possible post-thymic precursor T cells, whereas one patient with T-CLL had cells with the same phenotype (Leu-1+2a+3a-) as normal cytotoxic/suppressor T cells. The latter cells also expressed Ia antigens as defined by monoclonal anti-human Ia antibody. The remaining six cases, including one T-CLL and five ATL patients, had leukemic cells with the same phenotype (Leu-1+2a-3a+) as normally found on helper/inducer T cells, despite distinct clinical and immunological features between T-CLL and ATL. Some clinical findings observed in those patients may reflect functional activities retained by their leukemic T cells. (Author abstract) (34 Refs)

23. UTILITY OF MONOCLONAL ANTIBODIES IN THE IMMUNOLOGIC PHENOTYPING OF ACUTE LYMPHOBLASTIC LEUKEMIA.

Yu AL, Royston I, Leung KL, Kung FR, Hartman GA, Lightsey AL, Vangrove J, Sobol RE
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Hybridoma; 1(2):91-98 1982

Two monoclonal antibodies were used in conjunction with conventional lymphocyte markers to characterize acute lymphoblastic leukemia (ALL) in 34 children and 11 adults. Monoclonal antibody T101 detects a 65,000 mol wt cell surface antigen (T65) found on all T-cells in the peripheral blood and lymph node, T-cell lines, and thymocytes; the second antibody detects a monomorphic determinant on the Ia-like antigen, which is a bimolecular complex of 27,000 and 35,000 mol wt. Four distinct phenotypes were evident in the childhood ALL patients; the most common of these was observed in 22 patients. The marker profiles of the 11 adult patients exhibited the four phenotypes found in the childhood cases, and one additional phenotype. The most common phenotype, found in 6/11 patients, was the same as the most common phenotype in the childhood group. Reactivity with monoclonal anti-Ia and anti-T65 antibodies appears to define two distinct clinical subgroups of childhood ALL. The more common group was Ia+T65-and was characterized by an equal male:female distribution; younger age, lower leukocyte count, and lower incidence of organ involvement at presentation; and longer disease-free survival than Ia-T65+ patients. The less common Ia-

T65+ group was associated with male predominance, anterior mediastinal mass, high leukocyte count, organ involvement, and early treatment failure. Anti-Ia and T101 reactivity are apparently mutually exclusive in ALL, since no Ia+T65+ patients were identified. (24 Refs)

24. DIAGNOSTIC VALUE OF THE ENZYME-LINKED IMMUNOSORBENT ASSAY FOR DETECTION OF CANDIDA ALBICANS CYTOPLASMIC ANTIGEN IN SERA OF CANCER PATIENTS.

Araj GF, Hopfer RL, Chesnut S, Fainstein V, Bodey GP
Dept. Lab. Medicine, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
J Clin Microbiol; 16(1):46-52 1982

An enzyme-linked immunosorbent assay (ELISA) was developed for quantification of Candida albicans cytoplasmic antigen in sera of cancer patients. Elevated antigen concentrations were detected in 7/7 patients with proven disseminated candidiasis, 9/13 with suspected disseminated candidiasis, and 5/17 with fever of unknown origin. Antigen concentrations of less than 100 nanog/ml were detected in 6 patients with bacterial infection, 3 with aspergillosis, 4 with cryptococcosis, 3 with coccidioidomycosis, 6 with no infection, and 31 normal healthy adults. (31 Refs)

25. DIAGNOSTIC VALUE OF CRYPTOCOCCAL ANTIGEN IN THE CEREBROSPINAL FLUID OF PATIENTS WITH MALIGNANT DISEASE.

Hopfer RL, Perry EV, Fainstein V
Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX
J Infect Dis; 145(6):915 1982

Titers of cryptococcal antigen were determined in 680 samples of cerebrospinal fluid from 557 patients. Of 14 patients with positive results, only 9 patients had proven cryptococcal meningitis; false-positive results were obtained from 5 patients. In five of the nine patients with proven cryptococcal meningitis, the initial specimen was positive for cryptococcal antigen before any other laboratory tests (India ink preparations or cultures) were positive, although subsequent specimens were positive by India ink preparations and/or cultures. Of the 557 patients tested, only 26 had CLL; it is interesting that CLL was the most common underlying disease in the present group of patients. All five of the patients with false-positive results and three of the nine patients with proven cryptococcal meningitis had initial reciprocal titers of cryptococcal antigen of less than or equal to 8. Two of the patients with proven cryptococcal meningitis had subsequent titers of greater than 8. Tumors, metastases, or bacterial meningeal infections were present in all five of the patients with false-positive results. Titers of less than or equal to 8 must be carefully interpreted because other initial laboratory findings may not be helpful; in the present study, only one of the patients with proven cryptococcal meningitis had a low level of glucose and only four had greatly elevated levels of protein in their initial specimens. Although patients with malignant disease are predisposed to cryptococcal infection, the prevalence of this infection is very low. The cryptococcal antigen test has a relatively high rate of false-positive results, but it is helpful for early diagnosis of cryptococcal meningitis. (Author abstract) (3 Refs)

26. INFECTIOUS MONONUCLEOSIS IN A ADULT PROGRESSING TO FATAL IMMUNOBLASTIC LYMPHOMA.

Snydman DR, Rudders RA, Daoust P, Sullivan JL, Evans AS
New England Medical Center, Box 238, 171 Harrison Ave., Boston, MA, 02111
Ann Intern Med; 96(6,part1):737-742 1982

We report a case of infectious mononucleosis progressing to fatal immunoblastic lymphoma. The patient, a 44-yr-old man who may have had an immunoregulatory defect, failed to have an appropriate T-cell response to his Epstein-Barr (EB) viral infection. His active EB viral infection was manifest by seroconversion of IgM-viral capsid antibody and a greater than four fold rise in IgG-viral capsid antibody. Also, he transmitted his EB viral infection to his wife who became ill 1 mo after his death. Clinically the patient's illness was characterized by waxing and waning lymphadenopathy, persistent fever, diarrhea (similar to that associated with cholera), a coagulopathy, and gastrointestinal bleeding. The patient had pathologic findings of a diffuse immunoblastic lymphoma involving lymph nodes, small bowel, liver, pancreas, kidneys, lungs, and bone marrow. Immunoiogic cell markers showed the tumor to be polyclonal. (Author abstract) (23 Refs)

27. SERUM ALPHA-1-ACID-GLYCOPROTEIN, HAPTOGLOBIN AND C3 IN HODGKIN'S DISEASE. A COMPARISON WITH OTHER ACUTE-PHASE INDICATORS.

Gobbi PG, Merlini G, Parrinello GA, Cavalli P, Ascari E
Istituto di Patologia Medica I, Universita di Pavia, Policlinico S. Matteo, I-27100 Pavia, Italy
Acta Haematol (Basel); 67(4):255-262 1982

One hundred seven determinations of alpha1-acid-glycoprotein (alpha1S), haptoglobin (Hp) and complement fraction 3 (C3) were made in 85 consecutive patients with Hodgkin's disease, both in acute phase (77 measurements) and in complete remission (30 measurements). Only alpha1S and Hp showed much higher levels in untreated disease than in remission, and elevation of alpha1S in activity of the disease is correlated to advanced stages and - less significantly - to severe histology. The ability of alpha1S, Hp and C3 to discriminate between activity and remission was compared with that of erythrocyte sedimentation rate (ESR), alpha2-globulinemia (alpha2), fibrinogenemia (Fb), plasma copper (Cu) and iron (Fe), all data being collected at the same point in time in each patient. The well-known discrimination ability of combined Cu and Fe (75%) can be further improved by alpha1S (81%) much more than by Hp, C3, ESR, alpha2, and Fb singly computed and nearly up to the maximum allowed by the eight indexes together (82%). (Author abstract) (23 Refs)

28. HUMAN BLOOD LYMPHOCYTE SUBSETS SEPARATED ON THE BASIS OF NYLON ADHERENCE, SRBC AND EA ROSETTING: NATURAL CYTOTOXICITY AND CHARACTERIZATION WITH MONOCLONAL REAGENTS.

Masucci G, Masucci MG, Klein E
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Cell Immunol; 69(1):166-174 1982

Lymphocyte subsets were separated by nylon-wool adherence, E-rosetting, and presence of Fc-gamma receptor (as defined by EA-rosetting capacity), and characterized by reactiv-

ity with the following monoclonal antibodies: OKT3, OKT4, OKT8 (reactive with T lymphocytes and T-lymphocyte subsets). OKM1 (reactive with cells of myelomonocytic origin), and OKIa-1 (reactive with HLA-Dr antigens). The majority of the OKM1-positive cells were collected in the EA+ compartment of the E-, and low-avidity E+ subpopulations. In spite of the separation as E rosettes, the EA+ low-avidity E+ cells did not react with OKT3 and OKT4. However, a proportion of these cells reacted with OKT8. these cells had high anti-K562 cytotoxicity. the EA-receptor-negative part of the E-subset, which had less OKM1-positive cells, was also active against K562. Activated T cells may have contributed to the activity of this fraction, because OKT3-and OKIa-1 positive cells were present. When Daudi was used as target, only the EA-rosette-negative parts of the E- and low-avidity E+ subsets were lytic. This activity was more evident after IFN activation of the effector lymphocytes. After introduction of the markers defined by monoclonal antibodies the heterogeneity of the NK-active population was still a fact. At least three cell types defined by these reagents were enriched in the different cytotoxic fractions: OKM1-, OKT8-, and OKIa-1-positive cells. The fact that part of NK activity was exerted by cells separated on the basis of SRBC rosetting and in the SRBC rosette-negative subsets, a high proportion of the cells reacted with monoclonals, which define T markers, confirms previous suggestions that the majority of NK cells belong to the T lineage. (Author abstract) (27 Refs)

29. SURFACE IMMUNOGLOBULINS ON HAIRY CELLS OF 55 PATIENTS WITH HAIRY CELL LEUKEMIA.

Golomb HM, Davis S, Wilson C, Vardiman J
Box 420, 950 East 59th St., Chicago, IL, 60637
Am J Hematol; 12(4):397-401 1982

Surface immunoglobulins (SIg) were determined on peripheral blood samples from 55 patients with hairy cell leukemia (HCL) and on hairy cells from spleen preparations of 14 of these 55 patients. The patterns of SIg for HCL was compared to the patterns on peripheral blood leukemic cells from 39 patients with chronic lymphocytic leukemia (CLL) and 15 patients with poorly differentiated lymphocytic (PDL) lymphoma. Of the 55 HCL patients, 42 could be scored for individual heavy and light chains; 16 had only IgG, 14 had two or three heavy chains, 7 had only IgD, and 5 cases had no SIg and were E-rosette negative. This pattern was different from the B-cell pattern in CLL and PDL where there were few cases of IgG alone (5%) and many cases of IgM alone (50%). Surface marker profile did not correlate with survival in any of the sub-groups tested. HCL appears to be a B-cell lymphoproliferative disease in greater than 90% of cases; many combinations of heavy chains with only a single light chain can be demonstrated. (Author abstract) (14 Refs)

30. HUMAN B-CELL NEOPLASMS IN RELATION TO NORMAL B-CELL DIFFERENTIATION AND MATURATION PROCESSES.

Godal T, Funderud S
Lab. Immunology, Dept. Pathology, Norwegian Radium Hosp., Oslo, Norway
Adv Cancer Res; 36:211-255 1982

Functional studies related to human B-cell neoplasias are reviewed. The B-cell system is described, including its immunoglobulin (Ig) gene organization and expression, repertoire expression, surface markers related to B-cell development, and regulation of B-cell function. General features of B-cell neoplasms, the relationships of the neoplasms to B-cell development, clinical prognosis determinants, and subsets and neoplasms in the B-cell compartment are discussed. Topics discussed include simultaneous expression of IgM and IgD; expression of surface and other Ig classes and the functions of surface Ig; complement receptors and B-cell differentiation; B-cell proliferation and antibody production; and maturation of B-cell neoplasms. Chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and non-Hodgkins lymphomas (NHL) are discussed. Both in mouse and man there is considerable evidence for the existence of distinct functional subsets of cells in the B-cell compartment. B-cells are assumed to come from a single lineage, and during most stages of development they have multiple choices for further development, ie, they retain differentiation potential. On this basis a model of neoplastic transformation is proposed to account for the existence of multiple myelomas, NHL, CLL, and ALL. (285 Refs)

31. FUNCTIONAL PROPERTIES OF T CELLS IN PATIENTS WITH CHRONIC TGAMMA LYMPHOCYTOSIS AND CHRONIC T CELL NEOPLASIA.

Rumke HC, Miedema F, Ten Berge IJ, Terpstra F, Van der Reijden HJ, Van de Griend RJ, De Bruin HG, Von dem Borne AE, Smit JW, Zeijlemaker WP, Melief CJ

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J Immunol; 129(1):419-426 1982

The expanded T cell populations of 10 patients with either T gamma lymphocytosis (5 patients) or proven chronic T cell malignancy (5 patients) were analyzed with respect to functional activity in vitro, including proliferative responses to mitogens, cytotoxic activity (killer [K] and natural killer [NK] cell activity), and regulatory activity on pokeweed mitogen-(PWM) induced immunoglobulin (Ig) synthesis (help and suppression) in comparison with marker phenotypes. In each of the five patients with Tgamma lymphocytosis, only one out of three functionally distinct cell types was found: Tgamma-K cells, Tgamma-S cells, or Tgamma-NK/K cells, which mediated K-cell activity, suppressive activity and both NK and K cell activity, respectively. An expanded Tgamma-K cell population was demonstrated in three patients with neutropenia with or without recurrent infections. Tgamma-S cells were found in a patient with severe hypogammaglobulinemia, and Tgamma-NK/K cells in one patient with asymptomatic lymphocytosis. Tgamma-K and Tgamma-S cells had a similar surface-marker profile (E+ or E-, Fcgamma+, OKT1(-)3+4(-)8+I1-M1(-)), whereas that of Tgamma-NK/K cells was different (E+, Fcgamma+, OKT1(-)3(-)4(-)8-I1+M1+). Longitudinal studies of three untreated patients with Tgamma-K lymphocytosis showed that the abnormalities were persistent but not progressive. In contrast, five patients with chronic T cell malignancy (2 with T-CLL, 2 with cutaneous T cell lymphoma [CTCL], and 1 with T-PLL) all had progressive disease. The neoplastic cells in these cases were E+, Fc gamma-OKT1+4+6(-) with variable expression of the OKT3 and OKT8 markers. The only functional activity observed in these cells was suppressive activity by OKT3(-)4+8(-) cells from a patient with CTCL. (Author abstract) (50 Refs)

32. 'WALDENSTROM'S MACROGLOBULINEMIA' TERMINATING IN IMMUNOBLASTIC SARCOMA. A CASE REPORT.

Abe M, Takahashi K, Mori N, Kojima M
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Cancer; 49(12):2580-2586 1982

An autopsy case of 69-yr-old man with Waldenstrom's macroglobulinemia terminating in immunoblastic sarcoma is reported. In the course of this case, the appearance of plasmocytoid lymphocytes was initially observed in peripheral blood smears and bone marrow punctures, but lymph node biopsy and bone marrow aspirations performed in the terminal stage, as well as autopsy, revealed a diffuse monotonous proliferation of immunoblasts in the lymphoreticular tissues. With the immunofluorescence method and PAP method Taylor, IgM kappa type of immunoglobulin was demonstrated in the cytoplasm of the proliferating cells, and the electron microscopic enzyme-labeled antibody technique identified localization of the immunoglobulin in the nuclear envelope and rough endoplasmic reticula of the immunoblasts. The results indicate that the initial appearance of plasmocytoid lymphocytes in this case and its terminal transformation into immunoblastic sarcoma are rare phenomena occurring in a single clone proliferation disorder of B-cell synthesizing IgM kappa immunoglobulins. (Author abstract) (21 Refs)

33. PROGNOSTIC FACTORS IN PLASMACYTOMA.

Meusers P, Konig E, Brittinger G
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Med Klin; 77(10):321-325 1982

Diagnosis of plasmacytoma requires that at least two of three criteria be met: greater than 20% atypical plasma cells in the bone marrow, evidence of monoclonal immunoglobulins in the blood and/or urine, and osteolysis. Prognosis depends on the type of immunoglobulin produced by the tumor. The types, in order of decreasing prognostic chances, include IgG, IgA, Bence-Jones kappa, Bence-Jones lambda, and IgD. The level of immunoglobulin and the presence or absence of anemia, renal failure, or osteolysis, when taken individually, are of little prognostic value. Prognosis becomes progressively unfavorable with increasing tumor size. One staging system correlates size with clinical factors and with evidence of renal failure. Among patients with tumors of the same size, prognosis depends on the [3H]thymidine labeling index (TLI). The av survival time for Group I (Stage I or II with a TLI less than 1%) is 68 mo; for Group II (Stage I or II with a TLI less than 1% or Stage III with a TLI less than 1%) 41 mo; fo Group III (Stage III with a TLI greater than 1%) 15 mo. Response to therapy cannot be predicted from prognostic factors, but requires in vitro or in vivo tests of the cytostatic agent. Prognosis in individual cases can be determined within 6 mo. (13 Refs) (In GER)

34. B-CELL NEOPLASMS WITH HOMOGENEOUS COLD-REACTING ANTIBODIES (COLD AGGLUTININS).

Crisp D, Pruzanski W
(c/o Pruzanski), Wellesley Hosp., 160 Wellesley St. East, Toronto, Ontario M4Y 1J3, Canada
Am J Med; 72(6):915-922 1982

Among 78 patients with persistent cold agglutinins, 31 had lymphoma, 13 had macroglobulinemia of Waldenstrom, six had chronic lymphocytic leukemia and 28 had chronic cold agglutinin disease. The average age was over 60 yr. Patients with chronic cold agglutinin disease had more hemolytic crises, bleeding and Raynaud's phenomena, and less frequently lymphadenopathy or hepatosplenomegaly. The frequency of anemia, positive Coombs test results, cryoglobulinemia and Bence Jones proteinuria was similar in the various groups. Survival time from diagnosis was on av 2 yr in lymphoma, 2.5 yr in Waldenstrom's macroglobulinemia, more than 6 yr in chronic lymphocytic leukemia and more than 5 yr in chronic cold agglutinin disease. Anti-I were common in chronic cold agglutinin disease and rare in other groups. Anti-I and other cold agglutinins were rare in chronic cold agglutinin disease and common in lymphoma and Waldenstrom's macroglobulinemia. In chronic cold agglutinin disease, and in Waldenstrom's macroglobulinemia, cold agglutinins usually had kappa light chains -92% and 71%, respectively - whereas in lymphoma, 71% of cold agglutinins had lambda light chains. The type of light chains related to the specificity of cold agglutinins. Cold agglutinins were cytotoxic to autologous and allogeneic lymphocytes. Occasionally, more autologous than allogeneic cells were killed implying that the former may be precoated in vivo with the antibodies. In conclusion, conditions with persistent cold agglutinins are a spectrum that varies from 'benign' autoimmune-like chronic cold agglutinin disease to malignant lymphoma. Marked differences in the light chain type of cold agglutinins, specificity toward membranous antigens and severity of clinical manifestations were noted in benign and malignant varieties. (49 Refs)

35. SPECIFIC IN VITRO ANTIBODY RESPONSES BY HUMAN BLOOD LYMPHOCYTES: APPARENT NONRESPONSIVENESS OF PBL IS DUE TO A LACK OF RECIRCULATING MEMORY B CELLS.

Callard RE, McCaughan GW, Babbage J, Souhami RL
Immunology Unit, Dept. Medicine, Univ. Sydney, Sydney 2006, Australia
J Immunol; 129(1):153-156 1982

Peripheral blood lymphocytes from a number of individual donors were tested for in vitro antibody production to influenza or herpes viruses. All donors were primed, yet a small proportion either failed to respond or responded very poorly when tested in vitro. Reconstitution experiments carried out with E- (B cells and monocytes) and E+ (T) cells showed that the inability of nonresponder cells to make antibody in vitro resided exclusively with E- cells. It was concluded that the defect was in the B cell compartment. This conclusion was supported by further reconstitution experiments using E- and E+ cells prepared from blood, spleen, and lymph nodes from the same donor. Blood E- cells from nonresponders failed to make antibody when combined with either blood, lymph node, or spleen E+ (T) cells. By contrast, E- cells from lymph nodes or spleens responded normally when recombined with E+ cells from spleen, lymph node, or blood. These experiments showed that nonresponsiveness resided within the B cell compartment, and moreover, that it was confined to the blood, ie, to the recirculating lymphocyte pool. Apparently, recirculating memory B cells may be sequestered, under some circumstances, from the blood to other lymphoid tissues. Patients with untreated Hodgkin's disease were also investigated. Blood lymphocytes from these patients failed to make antibody in vitro to influenza or herpes viruses, whereas spleen cells obtained during staging laparotomy responded well. Again, the defect in the blood was found to reside exclusively with the B cell compartment. In contrast to normals, blood lymphocytes from most Hodgkin's patients were unresponsive in vitro to

several antigens. Thus, part of the pathology of this disease seems to be a lack of B cells in the blood that can make specific antibody in vitro. (10 Refs)

36. MOUSE ROSETTE (M ROSETTE) IN THE DIFFERENTIAL DIAGNOSIS OF LYMPHOPROLIFERATIVE DISORDERS.

Gabrielli A, Leoni P, Marchegiani G, Montillo M, Centurioni R, Montroni M, Danieli G
Istituto di Patologia Speciale Medica e Metodologia Clinica, Universita di Ancona, Ancona, Italy
Minerva Med; 73(20):1383-1390 1982

The capacity of a subpopulation of human B lymphocytes to form nonimmune rosettes with mouse red blood cells (M rosettes) was used for the differential diagnosis of B-cell lymphoproliferative diseases in 24 patients (12 men and 12 women, 51-77 yr old) with chronic lymphocytic leukemia (CLL), 7 with leukemic lymphoma (LL) and 3 with hairy-cell leukemia (HCL). Four of the 24 patients CLL were in Stage 0, 16 in Stages I-II and 4 in Stages III-IV. The percentages of M rosettes were distinctly increased in the patients with HCL and LL. The percentage of M rosettes remained extremely elevated at lymphocyte counts below 10,000/cubic mm. The absolute counts of lymphocytes carrying this membrane receptor was found to increase with increasing lymphocyte count, which is an expression of the neoplastic population, and with the advancement of the clinical stage according to Rai's classification. (11 Refs) (In ITA)

37. RELATIONSHIP OF PRETREATMENT LYMPHOBLAST PROLIFERATIVE ACTIVITY AND PROGNOSIS IN 97 CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA.

Dow LW, Chang LJ, Tsiatis AA, Melvin SL, Bowman WP
St. Jude Children's Res. Hosp., P.O. Box 318, 332 North Lauderdale, Memphis, TN, 38101
Blood; 59(6):1197-1202 1982

We have analyzed the pretreatment 3H-thymidine labeling indices in blood and marrow blast cells from 97 children with acute lymphoblastic leukemia (ALL) and circulating blasts. The median marrow labeling index (LI) was 6.2% (range 0.8%-32.7%) and the median blood LI, 3.2% (range 0.3%-20%). Blood LI was significantly correlated with leukocyte count and rosette-forming (E+) lymphoblasts but not with central nervous system leukemia or thymic mass at diagnosis. Marrow LI was related to E+ blasts only. In children with E+ leukemia, both blood and marrow LIs were significantly higher than values for other ALL subtypes (p less than 0.01) excluding undifferentiated ALL, which was characterized by an increased blood LI. Eighteen patients had a blood LI that either equaled or exceeded the marrow LI; apart from age, the clinical features, blast phenotypes, and treatment responses of this group were similar to those of patients with blood LI less than marrow LI. Among 51 patients assessed for treatment response, the estimated median length of remission was significantly shorter for those with a blood LI greater than 4% ($p = 0.002$) or a marrow LI greater than 6% ($p = 0.011$). By Cox-regression analysis, the pretreatment proliferative activity of blood and marrow blasts, unlike other initial features studied, added significant prognostic information to leukocyte count in these patients with circulating blasts. The findings provide a cogent explanation for the differential clinical responsiveness of commonly recognized ALL subclasses. (Author abstract) (30 Refs)

38. MOUSE RED CELL ROSETTE FORMATION AND THE COLCHICINE SENSITIVITY TEST: RELATIVE USEFULNESS IN THE DIFFERENTIAL DIAGNOSIS OF CHRONIC LYMPHOCYTIC LEUKAEMIA AND B LYMPHOCYTIC LYMPHOMA.

Sugden PJ, Lilleyman JS
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J Clin Pathol; 35(4):376-379 1982

Mouse erythrocyte (M) rosette formation and colchicine sensitivity were compared for their ability to differentiate chronic lymphocytic leukemia (CLL) from B cell non-Hodgkin's lymphoma (NHL) with overspill. Twenty-two cases of CLL and 8 of NHL were studied along with 31 normal adults. Results from the patients in both tests differed significantly from the controls but colchicine sensitivity failed to differentiate them further. M rosettes, on the other hand, while increased in some patients with NHL were, without overlap, much more numerous in those with CLL, and clearly distinguished the two conditions. A significant autolymphocytotoxic effect of plasma from both study groups was also noted which was not found in the controls. (Author abstract) (12 Refs)

39. STUDIES OF HUMAN NATURAL KILLER CELLS. II. ANALYSIS AT THE SINGLE CELL LEVEL.

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J Immunol; 128(6):2553-2558 1982

This report deals with the nature of conjugate-forming and lytic conjugate-forming lymphocytes, their relationship to natural killer (NK) cells, and the use of the lytic conjugate-forming cell (LCFC) assay with K562 as a measure of NK frequency in normal donors and cancer patients. Conjugate-forming cells (CFC) from granulocyte- and monocyte-depleted peripheral blood were found to be a heterogeneous population of lymphocytes that included cells forming E rosettes (T cells), EA rosettes (Fc receptor-positive cells), and cells positive for OKT3, OKT4, Mac-1, OKM1, and HNK-1. Very few surface immunoglobulin-positive cells were CFC. The CFC population was twofold to threefold enriched in cells positive for the monocyte/null cell markers OKM1 and Mac-1 and the NK cell marker HNK-1. Analysis of the LCFC showed a highly significant correlation between NK1 cytotoxicity and LCFC frequency, leading to the conclusion that LCFC are indeed NK cells, and that the frequency of LCFC vs K562 is an accurate measure of NK cell frequency. Comparison of NK frequency vs overall cytotoxicity of a group of well-defined normal donors indicated that the characteristic level of NK activity seen for different individuals was primarily due to differences in NK frequency. Two examples of abnormal NK function in patients were used to illustrate the potential of the technique. Both patients had markedly reduced cytotoxicity per effector cell, one with a comparatively high NK frequency in association with T gamma proliferation, and the other, a patient on immunosuppressive drugs, with a normal NK frequency. The combination of assays to measure NK frequency and overall NK cytotoxic activity will permit a better understanding of NK function in vivo. (Author abstract) (31 Refs)

40. CHRONIC LEUKEMIA WITH A HYBRID SURFACE PHENOTYPE (T LYMPHOCYTIC/MYELOMONOCYTIC): LEUKEMIC CELLS DISPLAYING NATURAL KILLER ACTIVITY AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY.

Schlimok G, Thiel E, Rieber EP, Huhn D, Feucht H, Lohmeyer J, Riethmuller G
Medical Clinic II, Langemarckstr. 11, 8900 Augsburg, W. Germany
Blood; 59(6):1157-1162 1982

A patient with chronic leukemia exhibited uncommon clinical features, such as hypergammaglobulinemia and activation of intravascular coagulation after low-dose irradiation of the enlarged spleen. By light and electron microscopy, the leukemic cells resembled large granular lymphocytes. The following markers were simultaneously expressed on their surface: receptors for sheep erythrocytes and the Fc part of IgG; common T-cell antigens as revealed by a heteroantiserum (HuTLA) and monoclonal antibodies (OKT3, T411); antigens shared by cytotoxic/suppressor T cells (OKT8, T811) as well as myelomonocytic antigens defined by the OKM1 and M522 monoclonal antibodies. The leukemic cells showed both spontaneous (NK) and antibody-dependent (ADCC) cytotoxicity, but they did not suppress B-cell differentiation in vitro. (Author abstract) (40 Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

41. TUMOR MARKERS.

Ewing HP, Newsom BD, Hardy JD
Dept. Surgery, Univ. Mississippi Sch. Medicine, Jackson, MS
Curr Probl Surg; 19(2):53-94 1982

Oncofetal tumor markers, other oncofetal antigens, placental proteins and hormones, ectopic hormones, lactation-associated protein markers, tumor markers produced in response to neoplasia, and multiple tumor marker screening are discussed focusing on clinical and surgical aspects of interest. Association of alpha-fetoprotein (AFP) not only with hepatoma, but also with tumors of germ cell origin and less frequently with carcinomas of the stomach is confirmed. AFP may be detected by a number of assay techniques, which vary in sensitivity. Carcinoembryonic antigen (CEA) assays are used in screening for malignancy, assesssing prognosis, detection of recurrent carcinoma, and monitoring response to therapy. Cigarette smoking is the most common reason for an elevated CEA titer in a patient without carcinoma. Association of colorectal carcinoma and elevated CEA titers have been confirmed in 80-97% of patients. Clear conclusions concerning the nature and clinical usefulness of fetal sulfoglycoprotein, pancreatic oncofetal antigen, and additional fetal antigens cannot presently be made. Neoplasms associated with human chorionic gonadotropin (HCG) are listed. The clinical usefulness of serial determination of nonectopic HCG has been well established. Criteria for establishment of ectopic hormone secretion and hormonal tumor markers associated with carcinoma of the lung are presented. Tumor markers produced in response to neoplasia are polyamines, nucleosides and nucleotides, and hydroxyproline. Many tumors may produce multiple markers. (213 Refs)

42. ALPHA-FETOPROTEIN (AFP) AND HUMAN CHORIONIC GONADOTROPIN (HCG) AS TUMOR MARKERS IN CASES OF INTRACRANIAL AND INTRASPINAL GERM-CELL TUMORS.

Gjerris F, Pelterasen B, Nielsen K, Arends J, Haase J, Lindholm J, Wewer U, Albrechtsen R
Neurokirurgisk afdeling 2092, Rigshospitalet, DK-2100 Copenhagen 0, Denmark
Ugeskr Laeger; 144(18):1296-1299 1982

Alpha-fetoprotein (AFP) and human chorionic gonadotropic (HCG) levels were determined in eight patients (4-28 yr old) with germ-cell tumors within the CNS. The tumors were localized in the pineal region in five patients, and in infratentorially, suprasellarly and lumbarly in one each. The tumors were classified histologically as germinomas, teratomas, yolk sac tumors, embryonic carcinomas and choriocarcinoma. All patients were subjected to surgery which was radical in 4/8, and to radiotherapy and two to additional chemotherapy. The serum AFP levels were elevated in 5/8 patients preoperatively and in 0/8 patients postoperatively. The AFP levels in the cerebrospinal fluid (CSF) were elevated in 1/3 patients tested preoperatively and in 0/3 postoperatively. The serum HCG levels were elevated in 4/8 patients preoperatively and in 5/5 patients postoperatively, even though elevated levels were found in 2/5 patients 1 and 5 days after surgery, respectively. The HCG levels in the CSF were elevated in 2/2 patients tested preoperatively and in 3/3 patients tested postoperatively. Five of the eight patients have been free from tumor recurrence for 0.5-2 yr. The findings show the normalization of the AFP and HCG levels in serum and CSP after treatment in all patients studied. (15 Refs) (In DAN)

43. SERUM BETA2-MICROGLOBULIN AND OTHER 'TUMOR ASSOCIATED' ANTIGENS IN PATIENTS WITH BRONCHOGENIC CARCINOMA.

Mordasini C, Riesen W, Morell A
(c/o Riesen) Inst. Clinical and Experimental Cancer Res., Univ. Berne, Tiefenau Hosp., CH-3004 Berne, Switzerland
Lung; 160(4):187-194 1982

Quantitative determination of beta2-microglobulin (b2m), carcinoembryonic antigen (CEA) and alphafetoprotein (AFP) was made in 51 patients (mean 60 yr old) with bronchogenic carcinoma. Mean concentration of b2m in patients with bronchogenic carcinoma was 2.47 mg/liter (l), compared to 2.10 mg/l in patients with lung tuberculosis or other non-neoplastic lung diseases. Normal blood donors of similar age had a mean b2m concentration of 1.92 mg/l. Of patients with bronchogenic carcinoma, males had slightly higher b2m levels than females; concentrations greater than 2.4 mg/l b2m were observed in 24 patients. Lung cancer patients and normal blood donors showed distinct age dependent increases in b2m, the latter to a lesser degree. No clear correlation between histologic type of tumor and b2m level was observed. The longest survival time was noted in patients who did not have elevated levels of b2m. Of all individuals with a plasma b2m concentration greater than 3.0 mg/l, 9/10 had bronchogenic carcinoma. In 50 patients with histologically or cytologically proven bronchogenic carcinoma, b2m greater than 3.0 mg/l was observed in 9, CEA greater than 10 nanog/ml in 15, and AFP greater than 5 nanog/ml in 1. No patient had elevated b2m and CEA, and only one had elevated AFP and CEA. Combined determination of b2m and CEA gave 48% positive results, compared to 30% when CEA alone was determined. AFP determination did not increase the percentage of positive cases. (35 Refs)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

44. ELEVATED NUCLEOSIDE EXCRETION BY PATIENTS WITH NASOPHARYNGEAL CARCINOMA: PRELIMINARY DIAGNOSTIC/PROGNOSTIC EVALUATIONS.

Trewyn RW, Glaser R, Kelly DR, Jackson DG, Graham WP, Speicher CE
Dept. Physiological Chemistry, Ohio State Univ., 333 West 10th Ave., Columbus, OH, 43210
Cancer; 49(12):2513-2517 1982

Nucleoside excretion was monitored in the urine of patients with nasopharyngeal carcinoma, a difficult malignant disease to diagnose at early stages. Separation and quantitation of nucleosides were accomplished by using high performance liquid chromatography. Significantly elevated nucleoside levels were found for patients with newly diagnosed and recurrent carcinomas. The magnitude and timing of the increases indicate the value of monitoring these levels for diagnostic/prognostic evaluations for nasopharyngeal carcinoma. (Author abstract) (17 Refs)

45. URINARY CYCLIC NUCLEOTIDES AND THE CYTOPATHOLOGY OF HUMAN UTERINE CERVICAL DYSPLASIAS.

Duttagupta C, Romney SL, Palan PR, Slagle NS
Dept. Gynecology and Obstetrics, Albert Einstein Coll. Medicine, Ullmann Building, Room 111, 1300 Morris Park Ave., Bronx, NY, 10461
Cancer Res; 42(7):2938-2943 1982

Blinded urinary assays for cyclic guanosine 3':5'-monophosphate (cGMP) and cyclic adenosine 3':5'-monophosphate (cAMP) were performed on 49 subjects with documented abnormal cervical cytology and 21 control subjects with normal cytology. A significant difference in the mean cGMP:cAMP ratios between the case and control groups was found. A significantly greater proportion of women with cytological abnormalities had a cGMP:cAMP ratio above the 0.2 level (p less than 0.001). Cases treated surgically for severe dysplasia or carcinoma in situ of the cervix revealed a significant postsurgical fall in the cGMP:cAMP ratios (p less than 0.025). The possibility of utilizing urinary ratios of cyclic nucleotides as an objective index in the detection, monitoring of progression, and therapy of preneoplastic cervical lesions is discussed. (Author abstract) (27 Refs)

46. THE ROLE OF A SERUM DNA-BINDING PROTEIN (64DP) IN THE DIAGNOSIS OF MALIGNANT NEOPLASMS.

Mitomi T, Nakasaki H, Tajima T, Ogoshi K, Tsuda M, Katsunuma T
Dept. Surgery, Sch. Medicine, Tokai Univ., 259-11 Isehara, Japan
Int Adv Surg Oncol; 5:245-259 1982

Role of the DNA-binding protein with mol wt 64,000 dalton (64DP) as a tumor marker in diagnosing and monitoring patients with malignant disease is described. 64DP was measured with column sodium dodecyl sulfate-polyacrylamide gel electrophoresis and a single radial immunodiffusion method. The elevation of serum 64DP in 96 patients with malignant disease over that observed in normal controls or in patients with nonneoplastic disease appeared quite significant. Serum 64DP levels in 26 patients with stomach carcinoma were categorized according to clinical stages. No clear correlation was observed between the levels of 64DP and the clinical stage. Twenty-nine patients were subjected to serial determination of serum 64DP to monitor the response to treatment. Serum 64DP showed a drop approx 3 wk after resectional treatment. The 64DP level did not appear to decrease to normal value even after complete removal of the malignant lesion by radical gastrectomy. Eleven patients with recurrent stomach carcinoma were tested for 64DP. The level ranged from 31-220 ug/ml in these patients. Approx half of the patients did not show elevation of 64DP levels. Patients with carcinoma of other organs showed preoperatively high values of 64DP with subsequent decreases 3-4 wk after successful surgical treatment. Analysis of the amino acid composition of 64DP indicated that it is rich in leucine, glutamic acid, and aspartic acid. Amino acids in lower amounts were tryptophan and cysteine plus cystine. (14 Refs)

47. SIGNIFICANCE OF THYROGLOBULIN AS A TUMOR MARKER IN THE SERUM OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA: LONGITUDINAL AND CROSS-SECTIONAL STUDIES.

Schatz H, Grebe S, Maser E, Teuber J, Horn W, Schroder O, Schatz C
III. Med. Univ.-Klinik und Poliklinik, Rodthohol 6, D-6300 Giessen, W. Germany
Klin Wochenschr; 60(9):457-464 1982

For evaluating the clinical significance of thyroglobulin measurements for the follow-up of patients with differentiated thyroid carcinoma, thyroglobulin was determined radioimmunologically during the past 2 yr (up to 12x) in 40 patients after withdrawal of thyroid hormone. Thyroglobulin values were compared with whole-body scintigrams after radioiodine. Thyroglobulin antibodies, which may interfere in the radioimmunoassay for thyroglobulin, were also estimated by a radioimmunologic method. In the majority of cases, thyroglobulin levels corresponded to the scintigrams, however, the thyroglobulin level appeared to be a more precise index for changes in tumor tissue mass. In one patient the scintigram was negative, whereas considerable amounts of thyroglobulin were measured in the serum: x-ray tomography revealed a lung metastasis in this case. On the other hand, thyroglobulin was undetectable in the sera of patients who exhibited distinct metastases in the scintigram. Thyroglobulin can be regarded as a tumor marker in patients thyroidectomized for differentiated thyroid carcinoma. However, its determination can certainly not replace whole-body scintigraphy as postulated by several authors, although thyroglobulin measurement appears to be superior to scanning in some cases. A combined application of iodine scanning and thyroglobulin radioimmunoassay is thus advisable in the follow-up of patients with differentiated thyroid carcinoma. (Author abstract) (18 Refs) (In GER)

48. FURTHER EVIDENCE FOR THE USE OF POLYAMINES AS BIOCHEMICAL MARKERS FOR MALIGNANT TUMORS.

Horn Y, Beal SL, Walach N, Lubich WP, Spigel L, Marton LJ
Dept. Oncology, Assaf Harofeh Hosp., Sackler Sch. Medicine, Zerifin, Israel
Cancer Res; 42(8):3248-3251 1982

One hundred ninety patients with a variety of tumors presented within a specified time period and fit a specified protocol. Multiple serial urinary putrescine, spermidine, and spermine levels were obtained in these patients, and their disease activity over time, defined as either active or nonactive, was determined by clinical examination, the results of laboratory

tests, and radiological criteria. Twenty-four-hr urine collections were used for analysis of polyamine levels. A linear mixed-effects model and the method of max likelihood estimation were used for statistical analysis. Statistically significant differences were found in polyamine levels between patients with active or nonactive disease for tumors of the breast, stomach, prostate, female genital tract, and a variety of metastatic carcinomas of unknown origin. There were 105 patients with these tumors; 319 polyamine determinations were obtained from this subset of patients. Our results suggest that serial determination of polyamine levels in urine may have clinical utility for monitoring the disease states for these tumors. (Author abstract) (14 Refs)

49. URINARY 6-HYDROXYMETHYLPTERIN LEVELS ACCURATELY MONITOR RESPONSE TO CHEMOTHERAPY IN ACUTE MYELOBLASTIC LEUKEMIA.

Trehan S, Rao N, Shetty PA, Noronha JM
(c/o Noronha) Biochemistry and Food Technology Div., Bhabha Atomic Res. Centre, Trombay, Bombay 400 085, India
Cancer; 50(1):114-117 1982

In our earlier study it was shown that patients with various types of cancer excrete 3-to 20-fold higher levels of urinary 6-hydroxymethylpterin as compared to patients with nonmalignant disease or normal volunteers. In the present study urinary 6-hydroxymethylpterin levels have been measured as an index of disease status in acute myeloblastic leukemic patients on antileukemic drugs. The daily excretory pterin levels and the values of respective blast counts have been graphically presented for four cases with the chemotherapeutic regimens. Remission of the disease was marked by a rapid drop in the urinary 6-hydroxymethylpterin levels and correlated very well with the percentage of blasts. In another study the percentage of blasts and the urinary 6-hydroxymethylpterin were determined simultaneously in four patients undergoing chemotherapy. The data conclusively show that the simple noninvasive determination of urinary 6-hydroxymethylpterin levels accurately and rapidly reflects the status of the disease under treatment and could conveniently be employed as a suitable index for monitoring the effect of chemotherapy as well as the condition of the residual extramedullary leukemic infiltration. (Author abstract) (10 Refs)

50. ANTIBODIES TO INTERMEDIATE FILAMENTS AS DIAGNOSTIC TOOLS: HUMAN GASTROINTESTINAL CARCINOMAS EXPRESS PREKERATIN.

Altmannsberger M, Weber K, Holscher A, Schauer A, Osborn M
(c/o Osborn), Max-Planck-Institute for Biophysical Chemistry, D-3400 Goettingen, W. Germany
Lab Invest; 46(5):520-526 1982

Twenty-five primary gastrointestinal carcinomas have been studied using immunofluorescence microscopy with affinity-purified antibodies to prekeratin and to vimentin. The tissues were alcohol fixed and paraffin embedded before use. In all cases (ie, 1 case of esophageal carcinoma, 7 stomach carcinomas, and 17 large bowel carcinomas) the tumor cells are stained by antibodies to prekeratin. In cases in which only very few tumor cells are present, such as signet ring carcinoma, immunofluorescence with prekeratin antibody provides an easy way to visualize single tumor cells. When the same specimens were tested with antibodies to vimentin, the tumor cells were unstained, and only the fibroblasts and vessels of the stroma were decorated. Four of the tumors were also negative when tested with antibodies specific for either desmin, or glial fibrillary acidic protein or neurofilaments. Three metastases to the abdominal region from tumors originating in the ovary, stomach, and large bowel were like the primary tumors in that the tumor cells were positive when stained with antibodies to prekeratin and negative when tested with the antibodies to vimentin. (Author abstract) (25 Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

51. A NEW GLYCOPROTEIN ANTIGEN COMMON TO TERATOCARCINOMA, VISCERAL ENDODERM, AND RENAL TUBULAR BRUSH BORDER.

Ozawa M, Yonezawa S, Sato E, Muramatsu T
Dept. Biochemistry, Kagoshima Univ. Sch. Medicine, 1208-1, Usuki-cho, Kagoshima, Japan
Dev Biol; 91(2):351-359 1982

Glycoproteins were purified from teratocarcinoma OTT6050 by affinity chromatography on Dolichos biflorus agglutinin-agarose. The rabbit antiserum raised against the glycoproteins defined a new antigenic marker after absorption with sheep erythrocytes and particulate fraction of the mouse liver. The antigen was detected on the visceral endoderm of 7-day-old embryos, on the tubular brush border of the kidney in adult mice and on certain endodermal cells of teratocarcinomas. Upon sodium dodecyl sulfate-gel electrophoresis, the antigens from teratocarcinoma OTT6050 and from the kidney migrated as band(s) of mol wt around 500,000. Although the antigens from the two sources were immunologically identical, they should be different in carbohydrate sequence as judged from their behavior upon affinity chromatography on lectin-agarose. (Author abstract) (29 Refs)

52. A MONOCLONAL ANTIBODY WITH ANTI-BURKITT LYMPHOMA SPECIFICITY. I. ANALYSIS OF HUMAN HAEMATOPOIETIC AND LYMPHOID CELL LINES.

Wiels J, Lenoir GM, Fellous M, Lipinski M, Salomon JC, Tetaud C, Tursz T
Laboratoire d'Immunologie Clinique, Institut G. Roussy, Rue C. Desmoulins, 94800 Villejuif, France
Int J Cancer; 29(6):653-658 1982

There is a hybridoma-produced monoclonal rat IgM (38-13) which appears to define a Burkitt's lymphoma-associated antigen (BLA). In this paper, we describe the reactivity of 38-13 with a panel of human hematopoietic and lymphoid cell lines. In indirect immunofluorescence (IF) assays, 15 of 26 Burkitt's lymphoma (BL) lines studied were clearly stained with 38-13 (from 13 to 100% positive cells) by microscope, with varying numbers of heavily labeled cells. In these positive cell lines, fluorescence-activated cell-sorter (FACS) analysis demonstrated that BLA was actually present on all the cells. Positive BL included Epstein-Barr virus (EBV) genome-carrying lines and EBV-negative ones; thus, BLA is not related to the presence of EBV. Most of the 15 BL cells that reacted with 38-13 contained a typical t(8;14) translocation, but had variant translocations such as t(2;8) and t(8;22). The cells were derived from BL patients of different geographical origins and clinical features. Four BL lines were poorly stained and seven were negative with 38-13 in IF assays. The 32 EBV-positive lymphoblastoid cell-lines (LCL) studied were negative. In three line pairs, consisting of a tumor line and an LCL from the same patient, only the BL line was demonstrated to react with 38-13. A

series of non-BL cells, including hematopoietic, lymphoid and solid tumor lines, all failed to react with 38-13. Various attempts to modulate the expression of BLA on BL cells were unsuccesaful. However, it cannot be ruled out that BLA is actually a transient B-cell differentiation marker. (Author abstract) (18 Refs)

53. S-100-LIKE IMMUNOREACTIVITY IN NEUROENDOCRINE TUMORS (MEETING ABSTRACT).

Ulich TR, Yang K, Wen DR, Cochran AJ, Lewin KJ
Division of Surgical Pathology, University of California, Los Angeles, CA, 90024
Gastroenterology; 82(5,part2):1200 1982

S-100 is an apparently unique marker for neural crest derived cells such as glial cells, Schwann cells, and melanocyte-derived cells. In view of the possible neural crest origin of carcinoid tumors, 15 formaldehyde-fixed, paraffin-embedded neuroendocrine tumors (11 gastrointestinal carcinoids, 2 pulmonary carcinoids, and 2 medullary carcinomas) were studied by the PAP technique with an antiserum to S-100. Eight tumors contained scattered cells that showed focal cytoplasmic immunoreactivity of variable intensity. Immunoreactivity was seen in a minority cell population of the tumor. Immunoreactivity was present in three types of tumor cells: Uniform polygonal cells within the center of tumor nests, columnar cells palisaded at the periphery of tumor nests, and dendritic cells within and around the periphery of tumor nests. These findings raise the possibility that S-100-like immunoreactivity is the expression of a neural crest histogenesis of carcinoid tumors. The histogenesis of neuroendocrine cells and tumors has been the subject of much controversy. These findings could also be explained by immunologic cross-reactivity between S-100 and a known or unknown neuroendocrine polypeptide hormone. (no Refs)

54. GANGLIOSIDE PATTERNS: NEW BIOCHEMICAL MARKERS FOR HUMAN HEMATOPOIETIC CELL LINES.

Rosenfelder G, Ziegler A, Wernet P, Braun DG
Pharmaceuticals Res. Labs., CIBA-GEIGY Ltd., CH-4002 Basel, Switzerland
JNCI; 68(2):203-209 1982

The ganglioside patterns from a representative collection of 20 human B-cell, T-cell, null cell, myeloid cell, and early erythroid cell lines were determined. Radioactive sugar-labeled gangliosides from cultured cells were extracted, analyzed, and quantitated by high-performance thin-layer chromatography (HPTLC) and high-pressure liquid chromatography, essentially according to the polarity of the oligosaccharide chain. The ganglioside labeling patterns of the human cell lines were in some cases extremely complex, since more than 100 components could be separated upon two-dimensional HPTLC, eg, in the case of a promyelocytic cell line. Each type of cell showed a characteristic pattern: Null cell lines were much less complex than T-cell lines, and myeloid and erythroid lines exhibited characteristic patterns as well. Although clearly distinguishable from all other cell lines, the B-cell lines showed a high degree of heterogeneity. Therefore, gangliosides can be expected to serve as additional markers to establish the origin of a cell line or to classify pathologic cell populations. (Author abstract) (42 Refs)

55. RECEPTOR BINDING AND PROCESSING OF EPIDERMAL GROWTH FACTOR BY HUMAN BREAST CANCER CELLS.

Osborne CK, Hamilton B, Nover M
Dept. Medicine, Univ. Texas Health Science Center, San Antonio, TX, 78284
J Clin Endocrinol Metab; 55(1):86-93 1982

Epidermal growth factor (EGF) stimulates the growth of human breast cancer cells (MCF-7). To better define the mechanisms for these effects, we studied receptor binding and subsequent processing of [125I]EGF in cells growing in monolayer culture under conditions in which an effect on growth is observed. Binding was temperature dependent and was higher at reduced temperature. At 37 C, binding rapidly reached a maximum (20-60 min) and then gradually decreased. Binding was slower at a reduced temperature. High affinity was demonstrated by the ability of unlabeled EGF to compete for [125I]EGF binding; half maximal displacement was observed at an EGF concentration that also resulted in half-maximal biological activity (1-2 ng/ml). Scatchard plots derived from these data or from those of studies using increasing concentrations of [125I]EGF were curvilinear and superimposable. Plots from binding data obtained at 0 C were also curvilinear, suggesting that the processing and degradation of tracer alone cannot explain this finding. Other peptides did not compete for EGF binding. During a 6-hr incubation, progressive degradation of [125I]EGF occurred on and/or in the cells, with prompt release of low mol wt fragments into the medium. Furthermore, during this time, the bound intact EGF became more resistant to dissociation by excess unlabeled EGF. Reduced binding (50%), not due to simple occupancy, was also noted during a 2-hr preincubation with unlabeled EGF, indicating down-regulation of receptor. These data suggest the following sequence of events. At 37 C, EGF rapidly binds to specific receptors on MCF-7 cells. The bound EGF becomes more and more difficult to dissociate from the cell, and the number of available receptors is reduced, implying sequestration in the cell membrane and/or internalization of the hormone-receptor complex. Gradually, EGF is degraded, and the products are released from the cell. Human breast cancer appears to be a target for EGF action. (Author abstract) (24 Refs)

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CLINICAL STUDIES ON ONCOFETAL PROTEINS AS BIOLOGICAL MARKERS OF CANCER

1. THE PROGNOSTIC VALUE OF CEA DETERMINATIONS IN THE PLASMA OF PATIENTS WITH SQUAMOUS CELL CANCER OF THE CERVIX.

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Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Cancer; 50(2):283-287 1982

One hundred and ninety-five patients with squamous cell cancer of the cervix have been followed for 2-4 yr. Pretreatment CEA determination was of prognostic value only in patients with early clinical disease. Serial determinations of CEA after primary treatment are of limited value in advanced stages. Sixty-five percent of patients developing recurrent cancer after initial therapy for Stage IB disease had plasma CEA levels exceeding 5.0 ug/l. In many of these cases the CEA elevation preceded the clinical diagnosis by several months. (Author abstract) (15 Refs)

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HE 20.3173/2:

2. DIAGNOSTIC ROLE OF ALPHA-FETOPROTEIN DETERMINATION IN SERUM OF PATIENTS WITH MALIGNANT TESTICULAR NEOPLASMS.

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Georgian Cancer Res. Center, Tbilisi, USSR
Urol Nefrol (Mosk); (3):23-26 1982

Diagnostic efficacy of determination of serum alpha-fetoprotein (AFP) was studied in 91 patients with testicular neoplasms. Among these patients, 17 had teratoblastomas, 5 had mixed tumors, 1 had embryonal carcinoma, 1 had chorioepithelioma, 60 had seminomas, 1 had fibrosarcoma, 4 had carcinomas, and 2 had adenomas. AFP levels were assayed by a conventional precipitation method and by indirect immunoautoradiography (IR) technique. Precipitation method showed presence of AFP in the serum of 8/17 patients with teratoblastoma and in 2/5 patients with mixed tumors. The use of IR technique in the patients with negative results of precipitation tests showed AFP in nine additional patients (7/9 with teratoblastoma and 2/3 with mixed tumors). The IR test also showed the presence of FAP in one patient with embryonal carcinoma. Successful treatment resulted in disappearance of AFP. Repeated elevation of AFP was indicative of metastases or recurrence. (14 Refs) (In RUS)

CLINICAL STUDIES ON ENZYMES AS BIOLOGICAL MARKERS OF CANCER

3. THE ROLE OF PROSTATIC ACID PHOSPHATASE IN THE INVESTIGATION AND TREATMENT OF ADENOCARCINOMA OF THE PROSTATE.

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Ann NY Acad Sci; 390:110-121 1982

Use of prostatic acid phosphatase (PAP) determinations in screening, staging, and monitoring therapy of adenocarcinoma of the prostate (ACP) is reviewed. At present, screening of men for ACP in unselected populations is not possible using immunological methods. However, in selected groups, such as those with undiagnosed nodules, the test may provide useful information. Measurement of serum PAP is routinely performed for staging and determining treatment protocols for patients with diagnosed ACP. An elevated PAP level may indicate high-secreting primary tumors, or the presence of micrometastases. When elevations are repeatedly found, extension of disease beyond the prostate capsule is probable. PAP is elevated in 69-92% of patients with advanced ACP. Factors which might influence PAP levels include tumor burden, tumor grade, secretory activity, and clearance rate of PAP from circulation. Anaplastic tumors exhibit a greater percentage of elevations compared with those of other histologic types. Usefulness of bone marrow determinations is limited. Determination of PAP in the serum and immunohistochemically is described. Experience with PAP determinations in patients treated with localized radiotherapy, 125I implantation, and hormones is reported. Immunological determinations may be useful for the study of prostatic epithelial cells and can help identify metastases of prostatic origin. In vivo localization with appropriate antibody and scanning may allow recognition of tumor deposits in lymph nodes and bone marrow and may clearly delineate local disease. (25 Refs)

4. THE APPROPRIATE USES OF PROSTATIC ACID PHOSPHATASE DETERMINATION IN THE DIAGNOSIS OF ADENOCARCINOMA OF THE PROSTATE.

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Ann NY Acad Sci; 390:100-103 1982

The relationship of prostatic acid phosphatase (PAP) in the prostate is discussed. Histochemical studies show PAP to be well distributed in the hyperplastic cells, but a comparison with normal cells does not suggest the concentration of the enzyme to be in excess of normal. Experience in examining serum PAP activity in patients with benign prostatic hypertrophy suggests that elevation is relatively uncommon. The varying histological nature of the prostatic adenocarcinoma (PAC) has to be considered when reviewing serum PAP activity. A selected group of 100 patients in whom the diagnosis of PAC, encompassing all the histological types, had been confirmed, was examined. The serum was carefully collected under optimum conditions. All the patients were not treated before the serum was drawn for assay. Results of the investigation comparing the radioimmunoassay, enzyme-linked immunoabsorbent assay, immunoenzymatic assay, and fluoroimmunoassay are presented. At the earliest stages of PAC, not more than 24% of the patients showed PAP activity above the upper limit of normal. The range of activity did not exceed twice the upper limit of normal, and the mean of the abnormal values was 1.1 ug/liter above the upper limit of normal suggesting that a small mass of malignant cells, possibly below 10(9), is responsible for the increase in activity. Assay of PAP by a specific and sensitive technique constitutes a necessary step in the evaluation of the patient suspected of PAC. (9 Refs)

5. PROSTATE-SPECIFIC ACID PHOSPHATASE VERSUS ACID PHOSPHATASE IN MONITORING PATIENTS WITH PROSTATE CANCER.

Killian CS, Vargas FP, Slack NH, Murphy GP, Chu TM, Romas NA, Bruce AW
Roswell Park Memorial Inst., Buffalo, NY, 14263
Ann NY Acad Sci; 390:122-132 1982

The prostate-specific acid phosphatase (PAP) immunoassay was compared with the acid phosphatase (AcP) chemical assay in monitoring 57 patients with early and 33 with advanced prostate cancer. Patients were compared with respect to detection of confirmed disease recurrence from the time of definitive therapy or the development of disease progression, the potential prognostic value of mean level of serial PAP and AcP activities, and responsiveness of the assay to the objective clinical status during therapy. Elevated PAP activity generally preceded the elevation of AcP activity and represented a more sensitive parameter for disease recurrence and progression in both groups of patients. Serial mean levels of PAP activity greater than the mean + three standard deviations were more predictive for disease recurrence and progression than those of AcP activity in both groups of patients. PAP was a more sensitive monitor for changes in objective treatment response than was AcP activity. PAP was more specific for prostate tissue than AcP, therby offering a reliable marker for identifying metastases of unknown origin or confirming metastases derived from a primary prostate tumor. While these results suggest that the PAP immunoassay is superior to the AcP assay, the reliability of PAP activity to accurately follow the clinical disease status remains to be established. (20 Refs)

6. ACID HYDROLASES AS MARKERS OF MATURATION IN B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA.

Grossi CE, Zicca A, Leprini A, Cadoni A, Pistoia V, Ferrarini M
Instituto di Anatomia Umana Normale della Universita, Via De Toni, 14, 16132, Genova, Italy
Blood; 60(1):220-227 1982

Malignant lymphocytes from 30 B-cell chronic lymphocytic leukemia (B-CLL) patients were studied for the cytochemical localization of two acid hydrolases, alpha-naphthyl acetate esterase (ANAE) and acid phosphatase (AT). The large majority of the cells stained for both ANAE and AP in 7 cases, for AP only in 18 cases, and were negative for both the enzymes in 5 cases. Ultrastructural analysis revealed that the cells that displayed more mature morphological features, such as well developed smooth and rough membrane compartments, were those positive for acid hydrolases. The ANAE and AP are expressed by B cells at late stage of maturation was confirmed by the finding that some lymphocytes and all of the plasmacytoid lymphocytes and plasma cells from Walderstrom's macroglobulinemia, from mixed cryoglobulinemia, and from multiple myeloma patients stained strongly for both ANAE and AP. Using the expression of acid hydrolases and certain ultrastructural features as markers of cell differentiation, it was possible to demonstrate a process of maturation within the single B-CLL clones with accumulation of the cells at stages that differed in the various cases. (Author abstract) (37 Refs)

7. VALUE AND DIAGNOSTIC SIGNIFICANCE OF SERUM LACTIC DEHYDROGENASE IN INTERNAL MEDICINE.

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Sem Hop Paris; 58(25):1543-1548 1982

Among 2,175 patients seen over the last 3 yr, 100 had supranormal serum lactic dehydrogenase activities. The case-reports have been analyzed. Nearly half the patients had a malignant disease. Among the remaining patients, 19 had a hepatic disorder, 7 had heart disease, and 27 had various other conditions. In comparison to other enzymes (alkaline phosphatase, gamma-glutamyl transpeptidase, transaminases) that were also routinely assayed in our patients, abnormal serum LDH activities are much less common and their significance is quite different. An increase in serum LDH activity indicates a serious condition, often with a fatal outcome. Each etiologic group has been analyzed to assess the characteristics of patients with increased LDH activity according to each etiology. Analysis of coincident abnormalities of the other enzymes listed above shows marked differences between etiologic groups; diagnostic accuracy can thus be enhanced in certain conditions. Most patients with malignancies had poorly differentiated tumors, with metastases: 28 had an epithelial tumor, with hepatic and/or bone metastases in 23 cases, 5 had cancer of the liver, 10 had a malignant hemopathy, and 4 had a sarcoma. Cancer of the lung is the most common malignancy and may be responsible for increased serum LDH activity even in patients without metastases. Serum LDH assay is of value for monitoring the course in patients with initially increased activities as it falls under effective therapy and rises during exacerbations. (23 Refs) (In FRE)

CLINICAL STUDIES ON HORMONES AS BIOLOGICAL MARKERS OF CANCER

8. PROGNOSTIC SIGNIFICANCE OF THE STEROID RECEPTOR CONTENT IN PRIMARY BREAST CANCER.

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Arch Gynecol; 231(3):185-190 1982

Estrogen receptor (ER) and progesterone receptor (PR) contents in the primary tumor, involvement of axillary lymph nodes, and menopausal status were studied in relation to recurrence and survival rates in 222 patients with primary breast cancer. Women whose primary tumor showed no ERs or PRs developed recurrent disease earlier, and in the first 5 yr, more frequently. With a median period of observation of 46 mo, the recurrence rate for ER-positive cases (36%) was about equal to that for ER-negative cases (39%), but the free interval (time between mastectomy and appearance of recurrence) was markedly shorter for patients with receptor-negative tumors. Even after 6.5 yr, the survival rate for patients with ER-positive tumors was better than for those with ER-negative tumors; a similar trend seemed apparent in relation to PRs. Survival and recurrence rates seem to be more favorable for patients with estrogen receptor-positive breast cancer. This expectation applies only for patients who receive no further treatment or who continue on a given therapy. (14 Refs)

9. SEX STEROID RECEPTORS IN DIVERSE HUMAN TUMORS.

Kobayashi S, Mizuno T, Tobioka N, Ichimura H, Samoto T, Tanaka H, Masaoka A, Wakabayashi S, Umemura S, Fukuoka H, Nagai H
Second Dept. Surgery, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Gan; 73(3):439-445 1982

The estrogen receptor was assayed in 8 intracranial meningiomas, 14 lung cancers, 3 thymomas and 2 malignant lymphomas using the dextran-charcoal method. Progesterone and androgen receptors were also assayed in all the cases of lung cancer. The estrogen receptor assay was positive in three meningiomas, two lung cancers, and all thymomas and malignant lymphomas. The androgen receptor assay was positive in one case of lung cancer but the progesterone receptor was negative in all assayed cases. No cases showed multiple receptor positivity. An antiestrogen (tamoxifen) was administered to one case each of intracranial meningioma and lung cancer with positive estrogen receptor. The receptor content was decreased to an undetectable level in the former after 4 mo of administration. This finding suggests the estrogen dependency of the tumor. The lung cancer patient, however, died 2 wk later without any evidence of hormone dependency. (Author abstract) (27 Refs)

10. URINARY ANDROGEN METABOLITES AND RECURRENCE RATES IN EARLY BREAST CANCER.

Thomas BS, Bulbrook RD, Hayward JL, Millis RR
Imperial Cancer Res. Fund, P.O. Box 123, London WC2A 3PX, England
Eur J Cancer Clin Oncol; 18(5):447-451 1982

Androsterone and aetiocholanolone was measured in urine specimens obtained from 218 women with early breast cancer. Patients who excreted less than the median amount of these steroids had a significantly higher recurrence rate (p less than 0.005) than patients excreting more than the median value. The

relationship between androgen excretion and recurrence is stronger in pre-menopausal women than in the post-menopausal group. The androgen assays are still associated with recurrence rates when patients are stratified by pathological stage, but no clear relationship was found with histological grade. (Author abstract) (23 Refs)

11. DOES THE ECTOPIC SECRETION OF ACTH EXIST?.

Vereshchagina GV
Res. Inst. Biological Testing of Chemical Compounds, Kupavna, USSR
Eksp Onkol; 4(3):11-19 1982

Incidence of various hormonal disorders in cancer patients is reviewed, with special emphasis on the ectopic production of ACTH. The criteria of ectopic ACTH syndrome include correlation between increased blood level of ACTH and growth of tumor; absence of direct involvement of adrenals or hypothalamo-pituitary region; presence of ACTH in the tumor tissue; arterio-venous gradient of ACTH concentration; ability of tumor cells to produce ACTH in vitro; changes in functional state of ACTH-secreting endocrine glands; and persistence of elevated ACTH concentration following removal of ACTH-secreting endocrine glands. (91 Refs) (In RUS)

12. ECTOPICALLY PRODUCED CALCITONIN IN HUMAN HEMOBLASTOSES.

Pfluger KH, Gropp C, Havemann K
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Klin Wochenschr; 60(13):667-672 1982

The incidence of elevated serum levels of immunoreactive calcitonin (CT) in human myeloproliferative and lymphoproliferative disorders was investigated. On the basis of twice the normal range, about 45% of patients with acute leukemia and blast crisis of chronic myelocytic leukemia (CML) showed elevated serum levels of CT. Markedly elevated levels (greater than 1,000 pg/ml) were only found in this group. Since immunoreactive CT dropped to normal or only slightly elevated levels in remission and increased again before or during relapse, serum CT levels seem to reflect the activity of the disease. However, in patients with chronic leukemia, Hodgkin's and non-Hodgkin's lymphoma, a lower incidence and only slightly elevated serum values were found. In addition, the mol wt of the proteohormone in serum specimen and cell extracts was investigated by gel chromatography. Besides physiological CT, different high-mol wt forms of the hormone could be demonstrated in serum and in cell extracts. Extracts of leukemic cells revealed higher molecular forms only. It is suggested that the proteohormone is ectopically produced by leukemic cells. (Author abstract) (27 Refs)

13. TRANSIENT RISE IN TUMOR MARKER AFTER INITIAL ADJUVANT CHEMOTHERAPY FOR TESTICULAR CANCER.

Wolf DJ, Williams JJ
Div. Hematology-Oncology, New York Hosp. Cornell Medical Center, New York, NY, 10021
Urology; 20(1):50-52 1982

A transient rise in the serum level of beta-HCG following adjuvant chemotherapy for Stage IIB embryonal testicular carcinoma was observed. This rise probably is a marker for the persistence of otherwise undetectable residual microscopic tumor. Conceptually, the occurrence of a rise in a tumor marker in this setting might help to identify those patients more likely to benefit from more intense adjuvant chemotherapeutic programs. (Author abstract) (5 Refs)

CLINICAL STUDIES ON IMMUNOLOGICAL MARKERS OF CANCER

14. INDUCTION OF CALL ANTIGEN AND TERMINAL DEOXYNUCLEOTIDYLTRANSFERASE IN NORMAL PERIPHERAL LYMPHOCYTES DURING PHA STIMULATION.

Jager G, Lau B, Dormer P
Institut fur Hamatologie, Landwehrstr. 61, D-8000 Munchen 2, W. Germany
Leuk Res; 6(3):421-423 1982

Normal peripheral mononuclear blood cells were stimulated with phytohemagglutinin (PHA) and the occurrence of terminal deoxynucleotidyl transferase (TdT) and common acute lymphoblastic leukemia (cALL) antigen were examined during a 7-day culture. A positive reaction with anti-cALL antigen was obtained in approx 50% of the cells. The positivity occurred on day 2 during culture and was present for only a short period. The reaction with anti-TdT antibody started on day 2 and the number of positively reacting cells increased until the end of culture. TdT positivity occurred before the cALL antigen could be demonstrated and disappeared after a short period in the second experiment. At the end of the culturing period a small portion of cells showed again a positive reaction with the anti-TdT antibody. The portion of cells reacting with the anti-cALL antibody never exceeded 30% and disappeared on day 3. The third experiment was comparable to the second one. In all three experiments the cALL antigen was demonstrable in a very early phase of the PHA culture and for a short period of time and preceded the max of the DNA synthesis between 60-72 hr. Comparison of results from the PHA-stimulated cultures with those obtained in diffusion chambers (DC) showed that in both culture systems the cALL as well as the TdT antigens are inducible, DC cultures giving a more uniform response. The factors causing the difference in behavior of the cells in the two culture systems are not yet known. (8 Refs)

15. INTERACTIONS OF C-REACTIVE PROTEIN WITH LYMPHOID CELLS.

James K, Baum LL, Vetter ML, Gewurz H
Dept. Immunology/Microbiology, Rush Medical Coll., Chicago, IL, 60612
Ann NY Acad Sci; 389:274-285 1982

The interactions between CRP and peripheral blood lymphocytes were investigated. CRP, in the presence of an appropriate ligand, bound saturably to a small percentage of normal PBL. The characteristics and optimal conditions for this binding were defined using several different assay systems. CRP was found to bind preferentially to cells with the IgG FcR. Binding was increased in the presence of acute phase sera, and higher numbers of cells binding CRP were observed in acute phase individuals. CRP and CRP-CPS had minimal effects upon lymphocyte responsiveness in vitro, although enhancing effects on MLC and CMC reactions, and a slight blastogenic effect, were observed. CRP antigenicity was detected on a small percentage of PBL, and treatment of PBL with anti-CRP and complement led to loss of NK reactivity, suggesting a possible association of CRP with this function. The functional expression of binding of CRP complexes, the relationship of the CRP-binding site to surface CRP antigenicity and the FcR, and the role of these factors in lymphocyte functions such as NK reactivity and recognition, are yet to be determined. (Author abstract) (26 Refs)

16. IMBALANCE OF T CELL SUBPOPULATIONS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA OF THE B CELL TYPE.

Herrmann F, Lochner A, Philippen H, Jauer B, Ruhl H
Dept. Hematology and Oncology, Klinikum Steglitz, Free Univ. Berlin, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany
Clin Exp Immunol; 49(1):157-162 1982

T cell enriched mononuclear cells from the peripheral blood of 20 patients with histologically and immunologically defined chronic lymphocytic leukemia of the B cell type (B-CLL) and 20 healthy individuals of various ages were investigated with T cell-specific monoclonal antibodies (OKT 4 and OKT 8) with regard to their subpopulation distribution. In B-CLL, a significant increase of lymphocytes reacting with OKT 8 could be demonstrated. Whereas there was a ratio of OKT 4 to OKT 8 of 1.72 in the control group, and OKT 4 to OKT 8 ratio of 0.67 was found in the B-CLL as a whole. With increasing clinical stage in accordance with the Rai scheme, a further displacement of this ratio in favor of OKT 8 positive cells was found. These results clearly show that, in peripheral blood of patients with B-CLL, an abnormal distribution pattern of circulating T cell subpopulations is present and that this also has prognostic relevance. (Author abstract) (24 Refs)

17. REDUCED T-COLONY FORMING CAPACITY IN B-CHRONIC LYMPHOCYTIC LEUKAEMIA. II. CORRELATION WITH CLINICAL STAGE AND FINDINGS IN B-PROLYMPHOCYTIC LEUKAEMIA.

Foa R, Lauria F, Catovsky D, Galton DA
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Leuk Res; 6(3):329-333 1982

T-colony growing capacity of samples obtained from 33 patients with B-cell chronic lymphocytic leukemia (B-CLL) and 5 with B-cell chronic prolymphocytic leukemia (B-PLL) was studied to investigate the correlation with Rai's clinical staging and the proportion of circulating T-lymphocytes with suppressor phenotype (T-gamma). All patients were untreated or had been off therapy for at least 5 mo. According to Rai's staging, 9 B-CLL patients had Stage 0 disease, 8 Stage I, 14 Stage II, and 2 Stages III-IV. The overall proportion of T-gamma cells was significantly increased in both B-CLL and B-PLL compared with normal controls. The proportion of T-lymphocytes with helper phenotype (T-u) was significantly reduced in both diseases. In B-CLL the mean number of T-colonies (mean 31 +-32.5) was significantly lower than with normal T-lymphocytes (mean 121 +-36.1). T-colony forming capacity was related to the clinical stage of the disease. Seven of the 9 Stage 0 samples gave rise to more than 50 colonies (77.7%), while only 5/24 Stages I-IV samples (20.9%) gave the same number of colonies. In four of the five B-PLL tested, the T-colony growth of the purified T-lymphocytes was markedly reduced. The T-colony numbers and the percentage of T-gamma cells were correlated in 26 patients with B-CLL and B-PLL. Results indicated that the T-colony forming capacity appears correlated to disease progression. (13 Refs)

18. COLONY-FORMING ASSAY FOR CIRCULATING CHRONIC LYMPHOCYTIC LEUKEMIA CELLS.

Taetle R, Richardson D, To D, Royston I, Mendelsohn J
Univ. Hosp. H720, 225 Dickinson St., San Diego, CA, 92103
Leuk Res; 6(3):335-344 1982

Adaptation of a technique for growth of B lymphocyte colonies to peripheral blood cells of 18 patients with clinically and pathologically typical chronic lymphocytic leukemia (CLL) is reported. T-lymphocyte-depleted CLL peripheral blood cells were cultured with irradiated, normal T cells, and media conditioned by normal, mitogen-stimulated T cells in methylcellulose. Small colonies of approx 40 cells appeared after 5-7 days incubation and little or no growth was noted in the absence of irradiated T lymphocytes. The relationship between the number of cells plated and number of colonies observed was linear over a wide range of plating concentrations. No correlation was observed between plating efficiency and the number of circulating leukocytes or lymphocytes. A high percentage of CLL colony-forming cells were synthesizing DNA (S phase). Cells harvested from normal T lymphocyte colonies were greater than 95% sheep red blood cell-rosette positive and greater than 95% positive when stained for OKT3 and/or T101, compared with less than 5% of cells harvested from CLL colonies. The presence of large numbers of surface immunoglobulin positive cells could not be demonstrated in CLL colonies. Drug sensitivity studies to adriamycin (ADM) and melphalan (ME) were performed on five patients previously treated with alkylating agents and five patients who were untreated. CLL colony-forming cells were relatively resistant to ADM, although untreated patients were less resistant than previously treated ones. Previously treated patients were also relatively resistant to ME. Results indicated that the reported system can be used to study regulation of CLL cell proliferation, and may have utility in predicting response to chemotherapeutic agents. (37 Refs)

19. IMMUNOSUPPRESSIVE EFFECT OF ACUTE-PHASE REACTANT PROTEINS IN VITRO AND ITS RELEVANCE TO CANCER.

Samak R, Edelstein R, Israel L
(c/o Israel) Laboratoire d'Immunobiologie des Tumeurs Humaines, Centre Hospitalier Universitaire Paris XIII, Hopital Avicenne, 125, route de Stalingrad, F-93000 Bobigny, France
Cancer Immunol Immunother; 13(1):38-43 1982

Several acute-phase reactant proteins (APRPs) were screened for their immunological effects to investigate immunosuppressive properties of serum from patients and animals with malignant disease. Concentrations used were determined by taking the highest levels observed in patients waith metastatic cancer, then preparing one-half, one-quarter, and one-eighth dilutions. In the lowest concentration tested (1), none of the proteins significantly modified the response of normal lymphocytes to the phytohemagglutinin (PHA). At concentration 2, haptoglobin and fibrinogen significantly decreased lymphocyte response. At the lowest concentration tested (2) none of the proteins significantly inhibited monocyte chemotactic migration. At concentration 3 orosomucoid became inhibitory, while at the highest concentration (4), both haptoglobin and fibrinogen became inhibitory. Orosomucoid, alpha1-antitrypsin, and ceruloplasmin did not significantly depress the blastogenic response individually at any of the concentrations tested nor when they were combined in concentration 1. When combined in concentrations 2-4, significant suppression of the blastogenic response was observed. The blastogenic response was maximal with a PHA dilution of 1/32. Preincubation of cells with a 1/32 dilution of PHA for 2 hr, followed by washing and post-incubation for 46 hr with phosphate-buffered saline produced a significant blastogenic response. When the post-incubation was performed with fibrinogen (concentrations 3 and 4) significant suppression was observed. (22 Refs)

20. EFFECTS OF DIPHENYLHYDANTOIN ON KILLER CELL ACTIVITY AND OTHER IMMUNOLOGICAL FUNCTIONS. A SEQUENTIAL STUDY INCLUDING THE INTERACTION OF CORYNEBACTERIUM PARVUM IN MELANOMA PATIENTS.

Thatcher N, Wan HH, Swindell R, Wilkinson PM, Crowther D
Dept. Medical Oncology, Christie Hosp. and Holt Radium Inst., Wilmslow Road, Manchester M20 9BX, England
Int J Immunopharmacol; 4(3):167-174 1982

The effects of a single dose of phenytoin (PHEN; 300 mg/square meter) upon killer cell (NK) cytotoxicity, serum immunoglobulins, and T and B cell proportions was investigated prospectively in 11 patients (6 males, 5 females) with metastatic malignant melanoma. No acute change in T lymphocyte rosettes, serum immunoglobulins, and DNA synthesis of lymphocyte cultures were observed after PHEN treatment. An early immunosuppression occurred within 10 hr after PHEN with reductions in lymphocyte count and NK activity. This suppression was reversible, with apparent recovery by 58 hr. Such a feature could explain the transient lymphadenopathy observed before cessation of PHEN medication. The profound and early immunosuppression associated with the first PHEN dose was abrogated by Corynebacterium parvum immunization (iv infusion 2 mg/square meter in 300 ml physiological saline over 3 hr) preceding a second dose of PHEN. While the second dose of PHEN caused some immunosuppression, no increase in T cells, NK, and phytohemagglutinin induced cytotoxicity above initial values was observed. (23 Refs)

21. CYTOTOXICITY OF NATURAL KILLER CELLS. CORRELATION WITH EMPERIPOLESIS AND SURFACE ENZYMES.

Burns ER, Zucker-Franklin D, Valentine F
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Lab Invest; 47(1):99-107 1982

Cell-mediated cytotoxicity involving natural killer cells requires contact between effector and target cells for effective cytolysis. Ultrastructural studies of biopsies of primary human malignant melanoma showed mononuclear leukocytes to be located in close proximity to tumor cells and, on occasion, within the confines of the melanoma cell itself. This phenomenon, called emperipolesis, was examined in vitro to determine whether the same population of cells that exhibits emperipolesis is responsible for cytotoxicity. Since natural killer cells have been identified morphologically and functionally as large granular lymphocytes with surface receptors for the Fc portion of immunoglobulin (FcR+ cells), lymphocytes were depleted of FcR+ cells, and their cytotoxicity and ability to emperipolese were measured. Both of these properties were markedly diminished (88 and 85%, respectively). Systematic comparison of emperipolesis and cytotoxicity from donors known to exhibit either high or low lymphocyte cytotoxicity showed perfect concordance. Ultrastructural analysis of in vitro emperipolesis revealed the emperipolesing lymphocytes to be FcR+ cells establishing identity with the large granular cells known to mediate cytotoxicity. The morphologic marker found in both FcR+ cells, purified by rosetting techniques, and in emperipolesed lymphocytes consisted of cytoplasmic parallel tubular arrays. Further studies designed to elucidate a mechanism for cytotoxicity and emperipolesis implicated cell surface proteases as mediators of these activities. Competitive inhibition of surface proteases with artificial and natural inhibitors markedly reduced both cytotoxicity and emperipolesis. Therefore, it is likely that lymphocytes that are FcR+ participate in cell-mediated cytotoxicity through mechanisms involving cell contact and enzyme-initiated damage of target cells. Emperipolesis represents one type of effector-target cell contact leading to cytotoxicity. (Author abstract) (43 Refs)

CLINICAL STUDIES ON MULTIPLE MARKER SYSTEMS IN CANCER DETECTION

22. MEDULLARY CANCER OF THE THYROID. CLINICAL FORMS. DIAGNOSTIC AND THERAPEUTIC APPROACHES.

Rougier P, Travagli J, Schlumberger M, Caillou B, Lacour J, Gardet P, Parmentier C
Institut Gustave-Roussy, 39-53, rue Camille-Desmoulins, 94805 Villejuif, France
Rev Prat; 32(29):1997-2003 1982

Medullary thyroid (MTC) is a rare tumor of the thyroid which does not take up Iodine and is not influenced by thyroid stimulating hormone. Initial symptoms may include cervical nodules or functional signs such as diarrhea and flush. Diagnosis and surveillance of MTC is based on thyrocalcitonin and carcinoembryonic antigen. Treatment of choice is surgical excision. In cases where familial form of MTC is prevalent, relatives of patients should be screened for the disease. Post-treatment prognosis is good. (19 Refs) (In FRE)

23. THE LIMITS TO THE RELIABILITY OF BIOLOGICAL TUMOR MARKERS IN NONSEMINOMATOUS TESTIS TUMORS.

Boccon-Gibod L, Elias D
Clinque Urologique, Hopital Cochin, 27, rue du Faubourg Saint-Jacques, 75674 Paris, France
Ann Urol (Paris); 16(4):219-220 1982

Before castration the levels of alphafetoprotein and chorionic beta-gonadotropin were normal in six patients of whom three had retroperitoneal metastases (RM). In nine patients (4 of whom were free of RM), levels of the markers were elevated. After castration, 3/10 patients with normal marker levels had RM. In five cases in which levels were elevated, all patients had metastases. No RM developed in patients whose levels normalized following castration. (10 Refs) (In FRE)

CLINICAL STUDIES OF OTHER BIOLOGICAL MARKERS OF CANCER

24. HYDROXYPROLINE EXCRETION IN THE DETECTION OF OCCULT BONE METASTASES FROM BREAST CANCER.

Rowse AD, Morrison MJ, Scott PH, Banks AJ, Roginski C
Queen Elizabeth Hosp. Queen Elizabeth Medical Centre, Birmingham B15 2TH, England
Oncology; 39(5):287-291 1982

When surgery fails to cure breast cancer it is due to disseminated micrometastases present at the time of operation. The measurement of urinary hydroxyproline (OHP) is a possible screening test for such metastases in bone. This study compares both a single and serial urinary OHP estimation with the axillary node status, the bone scan status and the subsequent clini-

cal course. A single measurement did not correlate with the axillary node or bone scan status, neither was there a relationship with the subsequent clinical course. Serial OHP estimations, every 3 mo for a yr, increased the accuracy of the test such that node-positive patients had higher excretions than node-negative patients (p less than 0.05). Patients who subsequently died with bone metastases tended to have a higher excretion than those who remained disease free, although this did not reach statistical significance. No relationship existed between serial OHP estimations and bone scan status. We consider the measurement of urinary OHP to be insufficiently sensitive to detect bone micrometastases and it is only raised when a substantial amount of bone is involved. (Author abstract) (18 Refs)

25. THE VALUE OF SERUM THYROGLOBULIN MEASUREMENT AS A MARKER OF CANCER RECURRENCE IN THE FOLLOW-UP OF PATIENTS PREVIOUSLY TREATED FOR DIFFERENTIATED THYROID TUMOR.

Roti E, Robuschi G, Emanuele R, Bandini P, Russo A, Riva P, Galassi E, Guerra UP, Manfredi A, Bozzetti A, Guazzi AM, Gnudi A
Cattedra di Endocrinologia e Patologia Costituzionale, Ospedali Riuniti, Via Gramsci 14, 43100 Parma, Italy
J Endocrinol Invest; 5(1):43-46 1982

The value of serum thyroglobulin (hTg) in detection of cancer recurrence was studied in 104 patients previously treated with surgical and 131I total thyroid ablation for differentiated thyroid cancer. In 87 of the patients with negative 131I total body scans (TBS), serum hTg was undetectable in 80%. In 57 patients with positive TBS, serum hTg was measurable in 72% of the patients, and undetectable in 20%. The results suggest that both serum hTg measurement and 131I TBS are useful in detection of thyroid cancer recurrence. (20 Refs)

26. USE OF IMMUNOFLUORESCENCE TESTS FOR TDT IN HUMAN HEMATOLOGIC MALIGNANCY.

Coleman MS, Hutton JJ
Dept. Biochemistry, Univ. Kentucky, Lexington, KY
Adv Exp Med Biol; 145:109-114 1982

In clinical samples (bone marrow, peripheral blood, testicular tissue, cerebrospinal fluid, and lymph nodes) terminal deoxynucleotidyl transferase (tdT) was detected by a quantitative radiometric assay and by an immunofluorescence assay. The quantitative assay utilized a homopolymer of av chain length (50 residues) and deoxy guanosine triphosphate. Both rabbit anti-calf serum and rabbit anti-human serum gave nearly identical results. An analysis of individual samples grouped by disease showed that no systematic error exists in detecting TdT protein. Shipment of samples significantly reduced positive immunofluorescence. (5 Refs)

27. IMMUNOCHEMICAL DEMONSTRATION OF AN OVARIAN CANCER-ASSOCIATED URINARY PEPTIDE.

Stenman UH, Huhtala ML, Koistinen R, Seppala M
I, II Dept. Obstetrics and Gynecology, Helsinki Univ. Central Hosp., SF-00290 Helsinki 29, Finland
Int J Cancer; 30(1):53-57 1982

Immunization with a peptide fraction from ovarian cancer urine resulted in an antiserum that reacts with a 6,000-dalton (6K) peptide. In urine from some patients with advanced gynecological cancer, the concentration of 6K peptide was high enough to be detected by immunodiffusion. By radioimmunoassay the levels in normal serum could be determined. The concentration in serum was 5-20 ug/l and that in urine 5-50 ug/l. Elevated levels were observed in urine from 5 out of 8 patients with ovarian cancer, 10 out of 14 patients with cervical cancer and 9 out of 14 patients with endometrial cancer. The highest level observed was 12,000 ug/l. High concentrations of the 6K peptide (100-300 ug/l) were observed in amniotic fluid from 14-16 weeks of pregnancy. Some tumor extracts also had a high concentration of the 6K peptide. No immunological relationship was observed between the peptide and known tumor-associated antigens or serum proteins. These results suggest that the peptide is a new oncodevelopmental peptide which may have significance as a tumor marker. (Author abstract) (17 Refs)

SELECTED PRECLINICAL STUDIES OF BIOLOGICAL MARKERS OF CANCER

28. ESTROGENS STIMULATE CELL PROLIFERATION AND INDUCE SECRETORY PROTEINS IN A HUMAN BREAST CANCER CELL LINE (T47D).

Chalbos D, Vignon F, Keydar I, Rochefort H
(c/o Rochefort) Unite d'Endocrinologie Cellulaire et Moleculaire, U 148 INSERM, 60, rue de Navacelles, 34100 Montpellier, France
J Clin Endocrinol Metab; 55(2):276-283 1982

The effects of estradiol (E2) on two cloned sublines derived from the T47D human breast cancer cell line have been studied in vitro. Cell proliferation was evaluated by DNA assay, cell counts, and thymidine incorporation. The rate of synthesis of proteins released into the cell culture medium was assayed by [35S]methionine incorporation and polyacrylamide gel electrophoresis, followed by fluorography. In clone 11, which contains estrogen and progesterone receptors, estradiol (1 pM-1 nM) stimulated cell proliferation 2-to 5-fold after a lag period of 6 days. Maximal stimulation was observed with 1% of 3% fetal calf serum and without added insulin. The effect of E2 was biphasic, since the growth rate was stimulated for E2 concentrations less than 10 nM and then progressively inhibited for higher concentrations. Dexamethasone, dihydrotestosterone, progesterone, and R5020 (at 1 nM or 1 uM) did not modify cell growth. The antiestrogen Tamoxifen (1 uM) inhibited the E2-induced stimulation and decreased the growth of control cells. Estrogen also stimulated 2-to 3-fold the synthesis of approximately 60K mol wt dalton proteins which were released into the medium. This effect was seen as early as 1 day of E2 treatment, and a plateau of stimulation was reached with 0.1 nM E2. By contrast, in clone f, which contains low concentrations of estrogen and progesterone receptors. E2 had no effect on cell growth and stimulated slightly the synthesis of a 55K protein. These results demonstrate that E2 is able to directly stimulate the proliferation of human epithelial breast cancer cells after having stimulated the synthesis of approximately 60,000 dalton proteins released into the medium. (Author abstract) (30 Refs)

29. A NEW MARKER FOR HUMAN CANCER CELLS. 1. THE CA ANTIGEN AND THE CA1 ANTIBODY.

Asball F, Brunwell ME, Harris H
(c/o Harris) Sir William Dunn Sch. Pathology, Univ. Oxford, South Parks Road, Oxford OX1 3RE, England
Lancet; 2(8288):1-6 1982

In a search for antibodies that might distinguish between malignant and non-malignant cells a panel of matched pairs of hybrid cells produced by fusion of diploid fibroblasts with malignant cells originating from a cervical carcinoma was used as a screen. Each pair consisted of a hybrid in which malignancy was suppressed and a malignant segregant derived from this hybrid. A monoclonal antibody, designated Ca1, was found that discriminated absolutely between the hybrids in which malignancy was suppressed and the malignant segregants. This antibody detected an antigen present in the cell membranes of a wide variety of malignant human cell lines but not of diploid human cell strains. The antigen was found in very low concentrations, if at all, in homogenates of normal adult or fetal tissues. It could be immunoprecipitated by the Ca1 antibody from extracts of malignant cells but not from extracts of non-malignant cells. After reduction, the immunoprecipitated antigen separated in sodium dodecyl sulfate acrylamide gels as two bands with approx molecular masses of 390,000 and 350,000. These two components had the properties of glycoproteins with a high carbohydrate content; both bound the Ca1 antibody. The antigenic determinant resisted boiling at 100 C and extraction by a range of organic solvents. The binding of the Ca1 antibody to the antigen was substantially reduced by treatment of the antigen with neuraminidase, and the antigenic determinant was largely destroyed by certain endoglycosidases and by extensive proteolysis. Pending its further characterization, this antigen has been called the Ca antigen. (Author abstract) (24 Refs)

30. CELL SURFACE ANTIGEN PHENOTYPES AND ENZYME EXPRESSION PATTERNS OF TWO MURINE T-CELL LYMPHOMAS DERIVED FROM EARLY AND/OR MATURE THYMUS CELLS.

Dulleus HF, Hilgers J, Van Basten CD, De Weger RA, De Heer E, Den Otter W
Dept. Pathology, State Univ. Utrecht, Pasteurstraat 2, 3511 HX Utrecht, The Netherlands
Leuk Res; 6(3):425-428 1982

Expression of cell surface antigens on SL2 and GRSL13 cells and enzyme cytochemistry of murine SL2 and GRSL13 lymphoma cells were investigated. SL2 lymphoma occurred as a spontaneous tumor in DBA/2 mice, and GRSL13 lymphoma occurred as a spontaneous lymphoma in GRS mice. While T200 antigen expression was high on both lymphomas, Thy1 was low on GRSL13 and high on SL2. Significant difference between the two lymphomas was obtained using antibodies 30-G12 (anti-T200) and 30-H11 (anti-glycolipid) with positivity on GRSL13 and no reaction on SL2; a reverse pattern was seen with antibodies 53-7.3 (anti-Lyt1) and 53-6.7 (anti-Lyt2). Since ThB and the glycolipid detected by antibody 30-H11 were expressed on bone marrow cells and since ThB was not expressed at all on peripheral T cells, the antigens are apparently characteristic for the more primitive cells in the thymic series. Results showed that GRSL13 represents a T cell of a more primitive immature type, while SL2 represents a more mature T cell. Enzymes present and clearly expressed in the lymphomas as well as the majority of thymus cells were acid phosphatase, beta-glucuronidase, non-specific esterase, and alphan-aphthyl-acetate-esterase. No clear difference was observed between the two lymphomas and the normal thymus cells. (17 Refs)

31. ANALYSIS OF HUMAN LEUKEMIA/LYMPHOMA CELL LINES WITH MONOCLONAL ANTIBODIES BA-1, BA-2 AND BA-3.

LeBien T, Kersey J, Nakazawa S, Minato K, Minowada J
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Box 609 Mayo, Minneapolis, MN, 55455
Leuk Res; 6(3):299-305 1982

Results of testing 67 human leukemia/lymphoma cell lines with monoclonal antibodies BA-1, BA-2, and BA-3 are reported. Monoclonal antibody BA-1 showed less than 20% binding to any of 20 T acute lymphoblastic leukemia (ALL) cell lines. Approx 15% of MOLT-10 cells were BA-1 positive when tested on several occasions. Analysis of the other 19 cell lines with BA-1 consistently gave 0% reactivity using direct immunofluorescence. Both BA-2 and BA-3 showed significant binding to 7/20 and 7/20 T ALL lines, respectively. Very little overlap in the reactivity of BA-2 and BA-3 with T ALL cell lines was observed; only RPMI-8402 and MOLT-10 reacted with both antibodies. Sixteen non-T ALL cell lines included both pre-B (cytoplasmic IgM+, surface Ig-) and non-pre-B (cytoplasmic IgM-, surface Ig-). With one exception the three antibodies reacted with all cell lines tested. In most instances greater than 90% of cells from a given cell line were strongly reactive with BA-1, BA-2, and BA-3. Twenty-four cell lines were established from patients with B ALL, non-Hodgkin's lymphoma, and Burkitt's lymphoma. All cell lines expressed varying amounts of surface Ig. BA-1 bound to 15 cell lines, BA-2 to 9, and BA-3 to 17 cell lines. No correlation was observed between antibody reactivity and expression of a particularly heavy or light chain class. Ba-1, BA-2, and BA-3 were assayed against seven leukemic cell lines of myeloid/monocytoid origin. BA-1 showed partial reactivity with the K-526 cell line, whereas BA-2 was reactive with most K-526 cells. BA-3 did not bind any of the seven cell lines. Thus, BA-1,-2, and-3 bind primarily, but not exclusively, to leukemias of B-cell lineage. (31 Refs)

32. CHARACTERIZATION OF THE RECEPTORS FOR IGE ON MEMBRANES ISOLATED FROM RAT BASOPHILIC LEUKEMIA CELLS.

Isersky C, Rivera J, Triche TJ, Metzger H
Section Chemical Immunology, NIADDK, NIH, Bethesda, MD, 20205
Mol Immunol; 19(7):925-941 1982

Mast cells, basophils and a tumor analog, rat basophilic leukemia cells, have a surface receptor for immunoglobulin E (IgE). Membranes from such cells should be highly useful for the study of how the alpha- and beta-subunits of the receptor interact with the plasma membrane and function therein. Membranes were prepared from rat basophilic leukemia cells. The cells were reacted with radioiodinated IgE to saturate a fraction of their receptors and the radiolabel was used as a surface marker. When isolated from sucrose gradients, 40 +-10% yields of plasma membranes were obtained and these were typically purified 13-fold with regard to cellular proteins. Unoccupied receptors for IgE were almost all recovered (as assessed on membranes solubilized with detergent) as were surface-labeled proteins in general. The membrane-bound IgE appeared fully exposed as assessed with anti-IgE antibodies but surprisingly 70-80% of the unoccupied receptors present were unable to bind IgE when unsolubilized vesicles were tested. By electron microscopy the preparations appeared free of recognizable intracellular organelles. Though some of the membranes appeared multivesicular many showed large breaks in continuity. Assessment of permeability, carried out on dextran gradients, indicated that a significant number (greater than or equal to 50%) of the IgE-carrying membranes are not sealed.

It is therefore most likely that both external and cytoplasmic aspects of the plasma membrane were exposed in many of the vesicles. Treatment of such membrane vesicles with trypsin or papain did not alter the apparent mol wt of the alpha-chain of the receptor or its binding activity for IgE. Additionally, when the vesicles were examined by enzyme-catalyzed iodination, no labeling of the receptor was observed under conditions where it is not labeled on intact cells (ie in the presence of IgE). These results suggest that either the alpha-chain of the receptor does not penetrate the membrane or that it cannot be modified by the particular probes we used. (Author abstract) (34 Refs)

33. GENERATION OF LONG-TERM T-LYMPHOID CELL LINES WITH SPECIFIC CYTOTOXIC REACTIVITY FOR A SYNGENEIC MURINE LYMPHOMA.

Eberlein TJ, Rosenstein M, Spiess PJ, Rosenberg SA
NIH, Building 10, Room 10N 116, Bethesda, MD, 20205
JNCI; 69(1):109-116 1982

The long-term in vitro growth in T-cell growth factor (TCGF) of murine cytotoxic T-lymphoid cells directed against syngeneic tumor antigens was investigated. C57BL/6 mice were immunized to syngeneic FBL-3 lymphoma by two ip injections of irradiated FBL-3 lymphoma cells. Splenocytes from these animals were injected into mice with disseminated lethal FLB-3 tumor. The injection of cyclophosphamide (Cy) plus immunized lymphocytes significantly improved survival with cure of 53% of 38 animals. In comparison, treatment with Cy alone resulted in 0 to 31 cured and treatment with Cy plus unimmunized cells resulted in 0 of 40 cured (p less than 0.0005). These in vivo immunized lymphocytes were reexposed to FBL-3 tumor in vitro for 5 days in lectin-free TCGF (LF-TCGF). Although in vivo and in vitro sensitized lymphocytes exhibited no cytotoxicity toward fresh FBL-3 tumor cells in an 18-hour 51Cr release assay, expansion of appropriately sensitized cells in LF-TCGF resulted in significant lysis of fresh FBL-3 tumor cells. This significant lysis was specific and lysed syngeneic FBL-3 but not syngeneic MCA-103 fresh tumor targets. This maximal specific cytotoxicity was maintained for 2.5 months. A screening assay was developed that permitted rapid identification and isolation of low-frequency cytotoxic clones with reactivity specific for FBL-3 tumor. Several of these cloned cells were grown for almost 3 months with maintenance of high degrees of specific lysis (as much as 4,500 lytic U/10(6) cells). These cytotoxic lines and clones will be of value for the study of tumor-host immunologic interactions and perhaps for use in adoptive immunotherapy. (Author abstract) (68 Refs)

34. NATURAL CELL-MEDIATED CYTOTOXICITY IN VITRO AND INHIBITION OF TUMOR GROWTH IN VIVO BY MURINE LYMPHOID CELLS CULTURED WITH T CELL GROWTH FACTOR (TCGF).

Kedar E, Ikejiri BL, Gorelik E, Herbermann RB
(c/o Herbermann) Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD, 20205
Cancer Immunol Immunother; 13(1):14-23 1982

Characteristics of mouse cultured lymphoid cells (CLC) derived from lymphoid cells of normal and tumor-bearing mice were examined, and their cytotoxic reactivity against a variety of lymphoid and solid tumors was assessed. Lymphoid cells obtained from the spleen of normal and tumor-bearing mice were cultured for various periods of time, in different culture vessels, in the presence of crude or mitogen-depleted T cell growth factor (TCGF) of mouse and rat origin. The growth pattern of various cultures was monitored 3x/wk by viable cell counting, and the results obtained with some of the splenocyte cultures are shown. All CLC cultures maintained by the periodic addition of TCFG showed a strong cytotoxic activity against most of the tumor target cells tested: fresh and cultured, syngeneic and allogeneic, lymphoid and solid, natural killer (NK)-sensitive and NK-resistant. Cultured M109 and MT were slightly more sensitive to killing, in general, than freshly harvested transplanted M109 or primary spontaneous MT. With most of the CLC, max cytotoxic activity was observed after 2-3 wk in culture. Several surface markers that have been associated with either cytotoxic T lymphocytes or NK cells were assessed. Results suggested that Thy 1.2 is present on the CLC at a lower density or is less accessible to antibody plus complement attack than on fresh T cells. In local Winn neutralization assays, BALB/c CLC afforded partial protection against a syngeneic lymphoma and carcinoma (M109) in BALB/c mice and against an allogeneic lymphoma (MBL-2) in C57BL/6 mice. Systemic administration of CLC to mice with established disseminated tumors showed a limited therapeutic effect in two experiments. (39 Refs)

35. IN VITRO PRODUCTION OF MONOCLONAL AND POLYCLONAL IMMUNOGLOBULINS BY PERIPHERAL BLOOD MONONUCLEAR CELLS IN HUMAN PLASMA CELL MYELOMA.

Peest D, Holm G, Mellstedt H, Pettersson D
Klinische Immunologie, Medizinische Hochschule Hannover, Postfach 610180, D 3000 Hannover 61, W. Germany
Scand J Immunol; 15(6):595-603 1982

The in vitro monoclonal and polyclonal immunoglobulin (Ig) production of peripheral blood mononuclear cells was studied in human multiple myeloma (4 IgG myelomas, 1 IgA myeloma) and in one patient with benign monoclonal gammopathy. Using an enzyme-linked immunosorbent assay with anti-class-specific antisera and antisera against idiotypic structures on the myeloma protein, it was possible to quantitate separately monoclonal and polyclonal Ig of the same class in cell culture supernatants. After stimulation with pokeweed mitogen (PWM) patients' cells produced lower amounts of polyclonal Ig than cells from healthy adults. In contrast, production of monoclonal Ig could not be enhanced by PWM. Moreover, the kinetics of monoclonal Ig production was different from that of polyclonal Ig. Myeloma cells contained large amounts of monoclonal Ig while their content of polyclonal Ig was low. A rapid release of preformed monoclonal Ig during the 1st day of culture was not inhibited by puromycin. A later phase of release was partly suppressed by puromycin and was probably caused by active protein synthesis. (Author abstract) (27 Refs)

36. ISOLATION AND CHARACTERIZATION OF A NEW FUCOGANGLIOSIDE ACCUMULATED IN PRECANCEROUS RAT LIVER AND IN RAT HEPATOMA INDUCED BY N-2-ACETYLAMINOFLUORENE.

Holmes EH, Hakomori SI
Div. Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Biol Chem; 257(13):7698-7703 1982

A novel fucoganglioside has been found to be accumulated in the liver of rats fed N-2-acetylaminofluorene before development of hepatoma. This new fucoganglioside persisted in hepatoma in vivo but was completely absent in normal rat liver as well as in livers of rats fed the nonhepatic carcinogen, acetylaminophenanthrene, and a tumor promoter, trichloro-2,2-

bis-(chlorophenyl)ethane. The ganglioside was isolated by high performance liquid chromatography and the structure was determined by methylation analysis, sequential degradation by various exoglycosidases, and by direct probe mass spectrometry of the permethylated derivative. This ganglioside, present in precancerous liver and in hepatoma in vivo, was identified as having a new structure with a substitution identical with blood group B determinant. A second fucoganglioside was detected in lower quantity in precancerous liver and in hepatoma in vivo but not in control tissue. This ganglioside co-migrated with the fucoganglioside isolated from H-35 hepatoma cells in vitro whose structure was identified as fucosylated GM1 ganglioside (Fucalpha1 to 2Galbeta1 to 4GalNAcbeta1 to 4 [NeuAcalpha2 to 3]Galbeta1 to 4Glcbeta1 to 1Cer). The results indicate that synthesis of new fucolipids is already induced at an early stage during the process of chemical carcinogenesis in rat liver which could be a unique membrane marker for diagnosis and therapy of a hepatoma and its premalignancy. (Author abstract) (45 Refs)

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